Summer 2012

A comparison of vibrotactile and air puff stimulation for inducing swallowing

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A Comparison of Vibrotactile and Air Puff Stimulation for Inducing Swallowing

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A dissertation submitted to the Graduate Faculty of

JAMES MADISON UNIVERSITY

In

Partial Fulfillment of the Requirements

for the degree of

Doctor of Philosophy

Communication Sciences and Disorders

August 2012

Dedication

This project is dedicated to my incredible family and friends for their constant love and support. Thank you to my parents, Rolfe and Sally White, and to my grandparents for their unconditional love, inspiration, and immeasurable support and belief in me. I would like to thank them for being such great role models, valuing my education, teaching me how to accomplish my goals, and encouraging me in everything I do. Thank you to my brother, Bryan White, and cousin, Andi Pollard, for their love, friendship, and prayers. Thank you to my friends for their support, optimism, giving me things to look forward to, and celebrating my accomplishments. And most importantly, I wish to thank my fiancé, Jeff Palmore, who has been there for me in all possible ways with love, patience, encouragement, and a smile. I am so excited about our future together!

Acknowledgments

I would like to acknowledge and thank the people who were important in the completion of this study. Thank you to my advisor, Dr. Christy Ludlow, who gave me the opportunity to work in the Laboratory of Neural Bases of Communication and Swallowing at James Madison University and to learn from her expertise, providing a strong scientific foundation. Thank you to Dr. Cynthia O'Donoghue for her leadership, advice, and time given to better my work. I would especially like to thank my mentor, Dr. Charles Runyan, for his guidance and friendship throughout my masters and doctoral programs. He has taught me far more than I could have hoped for. Thank you to the doctoral students in the Department of Communication Sciences and Disorders and the students in the Laboratory of Neural Bases of Communication and Swallowing who provided assistance, especially Lara Karpinski. I also wish to express my deep appreciation to Sarah Heygi for her expertise and friendship. Thank you to my parents who supported me every step of the way. And finally, thank you to God for answering prayers and giving me strength and skill I did not have on my own.

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Abstract

The purpose of this study was to evaluate the effectiveness of two types of non-invasive, sensory stimulation on increasing the rate of swallowing and for inducing cortical activity associated with swallowing. The types of stimulation investigated were vibrotactile stimulation to the external throat area surrounding the laryngeal tissues and oral air puff stimulation to the anterior faucial pillars. A functional near infrared spectroscopy (fNIRS) system measured relative changes in the concentration of oxygenated hemoglobin (HbO) in cortical sensorimotor regions as an indirect measure of brain activity. The experiment included 16 healthy adult participants between the ages of 28 and 60 years of age with no reported history of swallowing problems. Results indicated a significant difference between stimulation types on the frequency of swallowing. A significant change in the number of swallows was found between the air puff stimulation and control periods, while no difference was found between the vibrotactile stimulation and control periods. A significant main effect of type of stimulation ($p \leq .0005$) indicated that the two stimuli also differed in the effects on changes in blood oxygenation in the brain. Reduced concentration of HbO, particularly in the right sensory region, was seen during air puff stimulation compared to the control period. There was no overall difference in concentration of HbO in the cortical somatosensory and motor regions between the vibrotactile stimulation and control periods. Data recorded from fNIRS suggest an increased concentration of HbO in some participants during vibrotactile stimulation in the right sensory region which was positively related to the degree of increase in swallowing rate. The findings of an inverse blood oxygenation level at the cortex would suggest that although air pressure stimulation of the faucial pillars is upregulating swallowing at the brainstem level, it might interfere with cortical activation for swallowing when applied concurrently. The potential for cortical activation seen by vibrotactile device is important. If the vibrotactile device activates the cortex, the device could be used in targeted interventions aimed at enhancing voluntary swallowing control.

INTRODUCTION

Background of the Problem

Introduction to normal swallowing

To understand dysphagia, it is helpful to first understand the process of normal swallowing. Swallowing consists of three phases: 1) oral, 2) pharyngeal, and 3) esophageal. During the first phase, the oral phase, which includes the oral preparatory and oral transport phases, food enters the mouth and is formed into a bolus. With an upward and backward movement, the tongue pushes the bolus towards the posterior pharynx. The bolus enters the second phase, the pharyngeal phase, once the bolus passes the anterior facial pillars and the swallow reflex is triggered. In the pharyngeal phase, the bolus moves from the anterior facial pillars to the upper esophageal sphincter (UES) where it will enter the esophagus. Once the swallow is triggered, the motor activity of swallowing is a distinct, patterned sequence thought to be controlled by a bilateral central pattern generator (CPG) in the medulla at the level of the brainstem (Jean, 2001). The pharyngeal swallow reflex consists of several airway protection mechanisms. To prevent aspiration, swallowing usually occurs on exhalation, and respiration ceases for a moment of apnea during the swallow until exhalation resumes after the swallow (Perlman, Ettema, & Barkmeier, 2000). As the bolus enters the pharynx, velopharyngeal closure prevents material from entering the nasal cavity (Logemann, 1998). The larynx prevents material from entering the airway closing at the level of the true vocal cords, false vocal folds, and the aryepiglotic folds. The epiglottis also folds down to direct material away from the laryngeal vestibule. The larynx elevates and the UES relaxes to allow the bolus to enter the esophagus (Martin-Harris et al., 2005; Perlman, Palmer, McCullough, & VanDaele, 1999). In the final phase, the esophageal phase, the bolus enters the upper esophageal sphincter and a peristaltic wave action moves the bolus through the esophagus

and out of the lower esophageal sphincter into the stomach. Once the bolus has entered the UES, the larynx returns to its original position and respiration commences.

A swallowing disorder can result from dysfunction in one or more of these phases of swallowing. Patients are at risk of aspiration when something goes wrong in one or more of the stages and food or liquid enter the airway. The severity of dysphagia can range from mild to profound impairment. Moderate impairment involves some danger of penetration and aspiration into the airway, severe impairment has a serious risk of aspiration and penetration, and profound impairment is when the person is unable to safely swallow.

Swallowing frequency

The frequency of swallowing frequency is highly variable across individuals, with a mean swallowing frequency of 585 per day (range 203–1008) (Lear, Flanagan, & Moorrees, 1965). Swallowing frequency is dependent on state, occurring less often during sleep and more often during and after eating and drinking (Lear, et al., 1965; Lichter & Muir, 1975). Swallows occur approximately once per minute in alert states. Frequency of swallowing has been reported at 1.32 swallows per min with an error of 5.67 (Afkari, 2007). Another study found 1 swallow occurred every 2 minutes and 15 seconds ± 43 seconds (range of minutes, 1 minute and 20 seconds to 3 minutes and 32 seconds) (Vaiman, Nahlieli, Segal, & Eviatar, 2005). Several studies report that the volume of saliva in the oral cavity and the rate of salivary flow correspond with swallowing frequency; those adults with a faster rate of flow and/or more saliva in their oral cavity swallow more frequently (Kapila, Dodds, Helm, & Hogan, 1984; Rudney, Ji, & Larson, 1995).

Cortical, subcortical, and brainstem level control of swallowing

Swallowing is a complex sensorimotor act which consists of both volitional and involuntary activity involving highly coordinated neuronal activity at the cortical, subcortical,

and brainstem levels. Swallowing integrates sensory and motor components in order to execute the sequential movement of over 25 pairs of muscles as a bolus is formed, propelled, and enters the esophagus.

The oral phase of swallowing is a voluntary phase controlled by the cerebral cortex through the corticobulbar tracts. The cortical activation pathway includes descending impulses via the corticobulbar pathway to the reticular integrative region and the solitary-ambigual pathway that triggers the swallowing central pattern generator (CPG) at the level of the brainstem. The corticobulbar pathways are thought to be polysynaptic, and integrate cortical and brainstem regions involved in swallowing. Neuroimaging and clinic findings suggest that multiple regions of the cerebral cortex are involved in swallowing (Martin et al., 2007; Robbins, Levine, Maser, Rosenbek, & Kempster, 1993). The same cortical regions are implicated in swallowing in electrophysiological studies in primates and humans (R. E. Martin, Murray, Kemppainen, Masuda, & Sessle, 1997). Cortical regions found to be activated during swallowing include the lateral sensorimotor cortex, the premotor area, the anterior cingulate cortex, the supplemental motor area, the left pericentral and anterior parietal cortex, the insula, and operculum (Hamdy et al., 1999; Kern, Jaradeh, Arndorfer, & Shaker, 2001; Martin, et al., 2007; Martin, Goodyear, Gati, & Menon, 2001; Mosier & Bereznaya, 2001; Mosier et al., 1999; Mosier, Liu, Maldjian, Shah, & Modi, 1999; Toogood et al., 2005).

The pharyngeal phase of swallowing is under volitional and involuntary (reflexive) control by the central nervous system and the esophageal phase is under involuntary control by the central nervous system. The brainstem is responsible for the involuntary (pharyngeal and esophageal) phases of swallowing. Once the pharyngeal phase of the swallow is triggered, the sequence of movement is primarily controlled by the brainstem. The motor

activity of swallowing is a distinct, patterned sequence thought to be controlled by bilateral central pattern generators (CPGs) located within the pontine reticular system in the medulla oblongata at the level of the brainstem, receiving afferents from the periphery and from the cortex (Ertekin & Aydogdu, 2003; Hamdy, Aziz, Rothwell, Hobson, & Thompson, 1998; A. Jean, 2001). The dorsal medullary regions and the ventral medullary regions, both involved in swallowing, are located on both sides of the brainstem and are interconnected. The dorsal region in and next to the nucleus tractus solitarius and the medullary reticular formation contain the generator neurons involved in triggering and shaping the sequential swallowing pattern (A. Jean, 2001). The ventral region around the nucleus ambiguus contain switching neurons "which distribute the swallowing drive to the various pools of motor neurons involved in swallowing" (Jean, 1984, 2001).

Swallowing as an adaptable motor pattern

While there is a patterned motor behavior once the pharyngeal swallow is triggered, swallowing is not purely a brainstem reflex, unlike pupillary and cough reflexes. Cortical and subcortical pathways participate in a type of feedback loop with the CPG. Cortical and subcortical pathways may activate the CPG while sensory inputs along with the cortical and subcortical inputs modulate activity in the CPG. Thus, both peripheral and central nervous system inputs shape the patterned swallowing movements. Sensory feedback plays an important role in swallowing at the brainstem and cortical levels. Sensory input influences the brainstem central pattern generator involved in swallowing (Jean, 1990) and is also channeled to the cortical swallowing regions during the swallow (Jean, 2001; Lowell et al., 2008). Thus, sensory input modifies the swallow sequence as the bolus moves through the oral cavity and pharynx. The important role of sensory input has significant clinical

implications because it suggests dysphagia treatment involving stimulation of sensory receptors in the oropharynx can potentially modify the oropharyngeal swallow.

Sensory innervation of the oropharynx

Sensory innervation of the oropharynx plays an important role in swallowing. The sensory system is a part of the nervous system consisting of sensory receptors, neural pathways, and regions of the brain involved in sensory perception. Sensory receptors are sensory nerve endings and receive stimuli from the environment which are transported through neural pathways to the areas of the brain that process the information. When activated, sensory receptors convert information into electrical signals, or action potentials, that travel ascending pathways towards the central nervous system. The ascending pathways carry afferent information to the brainstem, deeper parts of the brain such as the thalamus, and the cerebral cortex.

The oral and pharyngeal cavities are dense in sensory receptor fields. Sensory receptors are in and below the mucosa of the oral cavity, oropharynx, pharynx and larynx (Jafari, Prince, Kim, & Paydarfar, 2003; Jean, 1984, 2001). Sensation to the faucial pillars, posterior pharyngeal wall, and posterior larynx can trigger a swallow, causing the CPG to produce the motor pattern for swallowing. The nerves providing the most afferent input to the swallowing CPG in the medulla are the internal superior laryngeal branch of the vagus nerve (CN X) (Sumi, 1977; Takagi, Noda, & Yamada, 2002), providing sensory input from the hypopharynx and larynx; and the glossopharyngeal nerve (CN IX) (Kitagawa, Shingai, Takahashi, & Yamada, 2002), providing sensory input from the faucial pillars. The facial nerve (VII) also supplies some sensory input to the swallowing center.

Different types of sensory receptors include: photoreceptors (light), mechanoreceptors (pressure or distortion), thermoreceptors (temperature), chemoreceptors

(odor or taste), and nociceptors (pain). A mechanoreceptor is a sensory receptor that responds to mechanical pressure from touch, pressure, stretching, and gravity. Oral chemesthesis occurs when chemicals activate thermoreceptors (temperature), nocioceptors (pain), and in some cases mechanoreceptors (touch) in the oropharyngeal mucosa and include sensations of burning, coolness, and tingling (Green, 2002).

Dysphagia due to cortical or subcortical damage

Intact cortical and brainstem control is needed for normal swallowing. The diverse location of brain lesions seen in patients with dysphagia exemplifies the complex cortical and subcortical involvement. Chronic dysphagia can result from a partial disconnection between the cortical swallowing areas and brainstem central pattern generator for swallowing (Aydogdu et al., 2001; Sacco et al., 1993). The importance of the suprabulbar regions (above the brainstem) in inducing a swallow is exemplified by the frequent occurrence of a delayed onset of the pharyngeal swallow in patients with cortical lesions (Veis & Logemann, 1985).

Reduced speed and coordination of hyolaryngeal elevation during the pharyngeal phase of swallowing increases the risk of aspiration in patients with dysphagia secondary to CVA or other neurological disorders (Logemann, 1988; Robbins, Logemann, & Kirshner, 1986). A lesion in the cerebral cortex or the brainstem can cause decreased range of motion of muscles of mastication, poor control of the bolus, residue on the palate, tongue, and in the buccal sulcae, and delayed initiation of the pharyngeal swallow, putting patients at risk for aspiration of food or liquid into the airway.

Changes in swallowing

Changes in swallowing associated with aging

Several studies have examined changes in swallowing associated with aging and found some changes in swallowing with age, particularly in those above age 60 (Rademaker,

Pauloski, Colangelo, & Logemann, 1998; J. Robbins, Hamilton, Lof, & Kempster, 1992; Tracy et al., 1989). Ekberg and Feinberg (1991) used videofluoroscopy and radiographs to look at swallowing in 56 people, mean age 83 years, with no symptoms of dysphagia and found "normal deglutition, as defined in young persons, was present in only 16%" of the participants. Researchers report that swallowing in older adults is characterized by longer durations and decreased efficiency (Martin-Harris, Michel, & Castell, 2005; Rademaker, et al., 1998). Changes in swallowing associated with aging include increased oral (Shaw et al., 1995) and pharyngeal transit times (Rademaker, et al., 1998; J. Robbins, et al., 1992); a normal delay in triggering the pharyngeal swallow (Logemann, 1998; Shaw, et al., 1995; Tracy, et al., 1989); decreased duration and width of the upper esophageal sphincter opening (Shaw, et al., 1995; Tracy, et al., 1989); reduced maximum vertical and anterior hyoid movement (Logemann et al., 2000); and an increase of oral or pharyngeal residue after swallowing (Logemann, 1998; Rademaker, et al., 1998). It is hypothesized that age-related diminishment of muscle mass and strength leads to reduced neuromuscular reserve in the swallows of older adults as compared to younger adults (Logemann, et al., 2000; Nicosia et al., 2000). Older adults are more likely to begin a swallow on inhalation instead of exhalation following the apneic moment that occurs during the swallow as compared to younger adults (Martin-Harris, Brodsky, et al., 2005). The differences in swallowing found in older adults are not necessarily suggestive of increased risk of penetration or aspiration (Martin-Harris, Brodsky, et al., 2005; J. Robbins, et al., 1992). However, aging is associated with disease that may lead to dysphagia, (Sonies, 1992) especially when disease requires older adults to use their neuromuscular reserve (Barczi, Sullivan, & Robbins, 2000).

Dysphagic stroke patients and pneumonia

As mentioned previously, patients with dysphagia who aspirate are at an increased risk of acquiring pneumonia (Smithard, O'Neill, Parks, & Morris, 1996). Stroke patients with aspiration are seven times more likely to develop pneumonia than those stroke patients without aspiration (Holas, DePippo, & Reding, 1994; J. Schmidt, Holas, Halvorson, & Reding, 1994). Smithard (1996) studied patients admitted with acute stroke and found that patients with dysphagia as evaluated on bedside assessment had "a higher risk of chest infection". Approximately 37 percent of stroke patients with dysphagia who experience aspiration will develop pneumonia (Doggett et al., 2001). Of note, dysphagia is one of the most important risk factors for pneumonia among elderly residents in long-term care facilities (Loeb, McGeer, McArthur, Walter, & Simor, 1999; Vergis, Brennen, Wagener, & Muder, 2001). Accordingly, the presence of dysphagia is a predictor of mortality, taking into account other factors such as weakness, neglect, hemianopia, incontinence, apraxia, age, and sex (Smithard, et al., 1996). Aspiration pneumonia has been estimated to inflict a 20% death rate in the first year following a stroke and 10-15% each year thereafter. It is usually not the first episode of aspiration pneumonia, but the subsequent recurrences over several years that eventually cause death (Schmidt, Smirnov, & Ryabova, 1988). The survival rate of patients at risk for aspiration is 17% over three years (Pick et al., 1996).

Current treatment of dysphagia

Speech language pathologists aim for patients' swallowing to be safe, efficient, and effective, to maintain adequate nutrition and hydration and to enhance quality of life (Marik & Kaplan, 2003). Current treatment of dysphagia includes restorative techniques and compensatory strategies. Restorative techniques include strengthening exercises, effortful swallow (patient squeezes hard with his throat and neck muscles during the swallow), the Mendelsohn Maneuver (patient holds the larynx up, either using the muscles of the neck or

with the hand, during the swallow for an extended period of time), thermal stimulation, and surface electromyography. Speech language pathologists may also train patients in use of compensatory strategies to swallow in a modified way in order to compensate for swallowing difficulty. Swallowing with a chin tuck is an example of a postural modification. Diet modifications (e.g., easier textures, such as thickened liquids, or nothing per mouth) are a type of compensatory strategy. Therapy can be divided into indirect and direct swallow intervention. Indirect swallow therapy teaches the patient exercises to strengthen impaired or weakened muscles without an actual bolus being introduced. In direct swallow therapy patients are taught exercises to perform while swallowing food or liquid. Tube feedings may be recommended to supplement or serve as an alternative to oral feeding, though the goal is typically to maximize oral versus non-oral feedings for enhanced quality of life.

Statement of the Problem

Because the pharyngeal phase of swallowing is reflexive and under automatic control of the brainstem central pattern generator in the medulla, chronic pharyngeal dysphagia is considered resistant to rehabilitation. Currently, the only intervention to reduce the likelihood of aspiration pneumonia in patients with chronic pharyngeal dysphagia is enteric feeding (tube feeding) to meet nutritional needs and provide adequate hydration.

Statement of the Need

It remains to be determined if augmenting sensory input would be helpful in facilitating swallowing. If so, researchers must determine the best way to deliver afferent information to the brain. Arguably, augmenting sensory input could potentially prove helpful in facilitating swallowing. As mentioned earlier, the nerves supplying afferent input to the swallowing centers in the brain are the internal superior laryngeal nerve, providing sensory

input from the hypopharynx and larynx, and the glossopharyngeal nerve, providing sensory input from the faucial pillars.

It is thought that stimulation to the glossopharyngeal nerve induces swallowing. Air-pulse stimulation has been shown to increase swallowing and activate the cortical regions associated with swallowing in healthy adults (Lowell, et al., 2008; Soros, et al., 2008). However, there are problems with the intraoral stimulation provided by the air puff. This cannot be applied while the patient is swallowing, as the delivery methods interfere with the bolus in the mouth. Furthermore, wearing the air puff delivery device is cumbersome. Thus, researchers are left to consider other types of stimulation.

Although stimulation of the faucial pillars can upregulate swallowing, it is unknown whether stimulation to the internal superior laryngeal nerve (iSLN) could also upregulate swallowing. Previous research has not yet demonstrated a way to stimulate mechanoreceptors in the iSLN noninvasively, in a way that could allow therapists to provide sensory input simultaneously while a patient is eating. The aim of the current investigation is to determine if stimulation of the iSLN also elicits swallowing in healthy adults and if the mechanoreceptors of the iSLN can be stimulated noninvasively in a way that may allow therapists to provide sensory input for swallowing *simultaneously* with eating.

The Specific Aims:

- Determine whether oral air puff stimulation to the anterior faucial pillars can increase the rate of spontaneous swallowing and induce cortical activity in the cortical regions for swallowing in healthy volunteers.
- Determine if an external vibrator on the throat area can increase the rate of spontaneous swallowing and induce cortical activity in the cortical regions for swallowing in healthy volunteers.

- Determine which stimulation type is more effective in increasing swallowing frequency.
- Determine whether oral air puff stimulation and/or vibratory stimulation can increase blood flow in the somatosensory and motor area of the cortex as measured non-invasively using functional near-infrared spectroscopy (fNIRS) and if it relates to the frequency of swallowing.

Purpose of the Study

The goal of the current research is to evaluate the effectiveness of two different non-invasive stimulation types (air puff delivered to the anterior facial pillars and a dime-sized external vibrator placed the throat) for increasing the rate of spontaneous swallowing and for inducing cortical activity in the cortical regions for swallowing in healthy volunteers.
It is hypothesized that:

Stimulation hypotheses

1. Frequency of swallowing will be greater during stimulation periods than during non-stimulation periods.
2. Frequency of swallowing with vibrotactile stimulation will be equal to the frequency of swallowing in the air puff condition.

Blood flow hypotheses

3. Blood flow will increase in the cortical somatosensory and motor regions during stimulation periods compared to the non-stimulation periods.
4. Blood flow will increase in the cortical somatosensory and motor regions during vibrotactile stimulation and during air puff stimulation.

The findings from the current research will determine if stimulation to the internal superior laryngeal nerve could serve to upregulate swallowing. These findings will set the foundation for future research concerning a non-oral stimulation approach to treatment to upregulate the swallow, one that could allow therapists to provide sensory input simultaneously during eating to patients with dysphagia. Future research could determine the effectiveness of vibrotactile stimulation to retrain swallowing through potential upregulation of swallowing used during mealtimes, and may prove beneficial for use with brain injured and stroke patients.

Limitations

Highly-pigmented (dark) skin color is an exclusion criterion because near-infrared spectroscopy requires the measurement of the degree of absorption of different wavelengths of light after being reflected back through the scalp. Dark hair and skin interferes with wavelength transmission, rendering the measurement of changes in absorption inaccurate, and reduces the signal to noise ratio for optical measurement of blood oxygenation (Wassenaar & Van den Brand, 2005).Though there were no volunteers with dark skin, if there had been they would not have been included as participants.

Review of the Literature

Reduced Sensory Input in the Laryngopharynx

This paper first reviews the evidence for the association between sensory input and swallowing.

Changes in oropharyngeal sensation

Changes in oropharyngeal sensation with aging

In addition to the loss of motor function seen in the aging and those with neurological problems, it is important to remember that sensory deficiencies can interrupt the normal pattern of swallowing (Jafari, 2003; Logemann, 1985). Sensation in the in the oral cavity, larynx, and pharynx is thought to diminish with age. On one hand, research studies examining a lingual two-point discrimination, temperature detection, and sensation of chemesthesis do not find a decline in oral sensation associated with aging in healthy adults under age 80 (Fukunaga, Uematsu, & Sugimoto, 2005). However, some researchers have found sensory discrimination in the area of the laryngopharynx diminishes with age. A progressive increase in sensory discrimination threshold with each decade of life can be seen with air pulse stimulation of the pyriform mucosa and aryepiglottic folds, innervated by the superior laryngeal nerve meant to elicit a laryngeal adductor reflex (which is a brief closure of the vocal folds) as a measure of determining larygopharyngeal sensory thresholds (Aviv, 1997; Aviv et al., 1994). The loss of laryngeal reflex with advancing age function can compromise airway protection and could contribute to dysphagia seen in the elderly. A decrease in myelinated nerve fibers is found in the superior laryngeal nerve, one of the two nerves providing the most afferent input to the swallowing CPG (Sumi, 1977; Takagi, et al., 2002), in adults over age 60. The timing of this decrease corresponds to the loss of sensory

input seen in larygopharyngeal sensory threshold testing (Mortelliti, Malmgren, & Gacek, 1990).

Changes in oropharyngeal sensation associated with neurological problems

Decreased oral, laryngeal, and pharyngeal sensation is often found in patients with neurological disorders, including stroke. Power et al. (2007) found bilateral reduced oral mechanoreception to electrical stimulation at the anterior faucial pillars in acute stroke patients. The laryngeal elevation delay is significantly correlated with oral sensation ($r = 0.5$, $p = 0.001$) (Power et al., 2007). Pharyngeal sensation deficits, independent of severity of stroke, are related to aspiration and pneumonia after stroke (Kidd, Lawson, Nesbitt, & MacMahon, 1993). Pharyngeal sensation was assessed with the tip of a stick applied to each side of the pharyngeal wall. Patients were asked to compare the two stimuli and researchers recorded the presence or absence of sensation. In the study, 80% of patients in whom sensation was lost on both sides and 66% of patients with sensation loss on one side aspirated, while patients with normal pharyngeal sensation did not aspirate. Additionally, stroke patients have decreased larygopharyngeal sensation in the laryngopharynx to air pulse stimulation meant to elicit a laryngeal adductor reflex (Aviv, Liu, Parides, Kaplan, & Close, 2000; Aviv et al., 1996). Aviv, et al. (2000) found that patients with bilateral, severe laryngopharyngeal sensory deficits have "a risk of laryngeal penetration that (is) five times that of those with no sensory deficits or moderate sensory deficits, and a risk of aspiration that (is) more than four times that of patients with no deficits or moderate deficits."

Reduced sensory input associated with dysphagia

Sensory deficits have been found in patients with laryngopharyngeal reflux and dysphagia (Aviv, et al., 2000). Researchers found sensory deficits in patients with reflux who had complaints of dysphagia. Additionally, dysphagia patients with severe sensory deficits

(defined by the absence of laryngeal adduction in response to endoscopic air pulses to the laryngeal mucosa) are significantly more likely to have aspiration and penetration than dysphagia patients without sensory deficits (Setzen, Cohen, Mattucci, Perlman, & Ditkoff, 2001).

Reduced sensory input in healthy volunteers

Reduced sensory input can disrupt swallowing in healthy volunteers. Some investigators have found surface anesthesia on the oral and pharyngeal mucosa delays the swallow, reduces volume per swallow and causes dysphagia (Mansson & Sandberg, 1974). Other researchers have not confirmed these results, finding limited effects of surface anesthesia on swallowing with coaching regarding timing of bolus management to resolve cases of trace aspiration or pooling (Ali et al., 1994; Bastian & Riggs, 1999).

Bilateral chemical nerve block of the internal superior laryngeal nerve has been shown to produce more effortful swallowing and an increased risk for laryngeal penetration and aspiration (Jafari, et al., 2003; Sulica, Hembree, & Blitzer, 2002). While an internal superior laryngeal nerve block has no effect on the motor components of swallowing, dysphagia results from a loss of the sensory component. Using fiberoptic endoscopic examination of swallow (FEES), Sulica et al. (2002) compared 30 swallows of thin liquids and puree without de-nervation to 30 swallows after a bilateral superior nerve block. All swallows before anesthesia were normal, while anesthetized subjects had significantly higher ($p < .05$) incidences of premature spillage, pharyngeal residue, and laryngeal penetration and aspiration. Jafari et al. (2003) anesthetized the ISLN bilaterally in 16 healthy normal subjects and found that 15 out of 16 subjects experienced penetration and all subjects reported effortful swallows. Of the total number of swallows in the anesthetized subjects, there was a 43% penetration rate, in contrast to a 1.4% penetration rate in the controls who were either

injected with saline or who received no injection. In the anesthetized subjects, there was an overall aspiration rate of 24% while the control group had no aspiration. These studies demonstrate that swallowing deficits accompany reduced laryngopharyngeal sensation and suggest there is a strong association between hypopharyngeal sensory deficits and motor function deficits. The sensory input from the iSLN is important if not crucial for laryngeal protection and a loss of sensory input in humans disrupts control of volitional swallowing.

Sensory stimulation can augment volitional control of swallowing

Sensory input and swallowing in animals

Sensory stimulation can augment volitional control of swallowing. In animals, electrical stimulation of the pharyngeal branch of the glossopharyngeal nerve or the internal superior laryngeal nerve (30–50 Hz) induces swallowing (Doty, 1951; Kitagawa, et al., 2002; Miller, 1972a; Sinclair, 1971).

Sensory stimulation in humans

Mechanical stimulation of the faucial pillars initiates the swallow reflex (W. T. Pommerenke, 1927). Sensory input from unilateral or bilateral air puffs to the oropharynx, innervated by the glossopharyngeal nerve, increases the frequency of swallowing and the urge to swallow in healthy adults (Soros et al., 2008; Theurer, Bihari, Barr, & Martin, 2005; Theurer, Czachorowski, Martin, & Martin, 2009). Older adults also show increased swallowing rates in response to oropharyngeal air-pulse stimulation (Theurer et al 2009).

Manipulated sensation and cortical response

A loss of sensory input reduces cortical activity in regions associated with swallowing. A magnetoencephalography (MEG) study illustrated that topical oropharyngeal anesthesia leads to decreased cortical activation in the primary sensory and motor cortex compared to swallowing without anesthesia (Teismann et al., 2007).

Additionally, sensory input to the oropharyngeal regions, particularly the faucial pillars, activates cortical regions associated with swallowing (Lowell, et al., 2008; Soros, et al., 2008). Stimulation from a plastic rod connected to a servo-controlled mechanical stimulator to the glossopharyngeal nerve afferents via input at the anterior faucial pillar elicits cortical responses as seen in glossopharyngeal evoked potentials (Fujiu, Toleikis, Logemann, & Larson, 1994). Air puffs delivered to the oropharynx activate core areas of the somatosensory system, including the thalamus, the primary somatosensory cortex, and classical motor areas such as the primary motor cortex and supplementary motor areas (Soros, et al., 2008). Air pulse stimulation activates much of the cortex that is activated during swallowing. The pattern of brain activity during air puff stimulation is similar to that of overt swallowing (Lowell et al., 2008; Soros et al., 2008). However, far too little attention has been focused on the cortical response to other types of stimulation.

Vibrotactile Device and Swallowing

Underlying mechanisms for the development of vibrotactile stimulation

Extensive animal research has demonstrated that the brain stem central pattern generators for swallowing in mammals can be actively controlled by stimulation of afferents in the internal branch of the superior laryngeal nerve, which innervate the mechanoreceptors in the laryngeal mucosa (Miller, 1972a). Electrical stimulation of the superior laryngeal nerve at 10-30 Hz produces fictive swallowing in cat and guinea pig animal models (Dick, Oku, Romaniuk, & Cherniack, 1993; Sugiyama et al., 2011). Activation of the swallowing central pattern generator through superior laryngeal nerve afferent stimulation for inducing swallowing was recently shown to involve neurons in the nucleus tractus solitarius and the reticular formation (Sugiyama et al., 2011). Although stimulation of the glossopharyngeal afferents has been used to increase the frequency of swallowing in humans, this mode of

stimulation cannot be used during swallowing as it requires an air puff stimulation, which interferes with by food or liquid in the mouth and therefore is not an effective method for swallowing retraining while eating. Animal research has already shown that stimulation of the afferents contained in the superior laryngeal nerve is a more potent stimulation for triggering swallowing than stimulation of the glossopharyngeal afferents in the faucial pillars alone (Chi-Fishman, Capra, & McCall, 1994).

Accessing the mechanoreceptors in the laryngeal area innervated by the superior laryngeal nerve has been the obstacle to the use of this type of stimulation for inducing swallowing in patients. Its deep position in the neck makes it difficult to access. Mechanoreceptors in the internal superior laryngeal nerve fibers in cats and rabbits respond very accurately to touch and pressure (Davis & Nail, 1987). A study by Davis and Nail demonstrate that vibratory stimulation to the laryngeal mucosa produced prolonged non-adapting neural responses in fibers of the superior laryngeal nerve (1987). This prompted the researcher to the selection of vibration as a stimulus in the current study. Prior to the current study, researchers have not stimulated mechanoreceptors in the laryngeal mucosa in humans to determine whether the iSLN will be activated and send afferent information to the swallowing CPG in the brainstem and the cortical regions associated with swallowing. By vibrating the thyroid cartilage, attached tissues around the thyroid (mucosa) will also vibrate, non-invasively stimulating the mechanoreceptors in the laryngeal mucosa. When applying vibration to the skin overlying the thyroid cartilage, the researcher verified that the vibration extended into the laryngeal mucosa by having the volunteer produce voicing and heard the vibratory stimulation in the voice. This demonstrated that the mechanoreceptors in the laryngeal mucosa would be activated by such a stimulus. Thus, clear evidence of activation of the central pattern generator for swallowing in the medulla in animals during superior

laryngeal nerve stimulation and the investigation of external vibration applied to the thyroid cartilage for the potential to stimulate this system noninvasively in humans were the bases for the development of this innovative concept for triggering swallowing in humans.

There are several potential advantages of vibrotactile stimulation. Vibration can be placed on the skin over the thyroid cartilage to stimulate the laryngeal mucosa innervated by the superior laryngeal nerve. Vibratory stimulation could be applied externally, so it does not interfere with swallowing in the oral cavity.

The vibrotactile device in this study was developed by Ludlow and colleagues (2007). .The dime-sized device administers low frequency (4 Hz) modulation of 100 Hz vibration to provide non adaptive mechanical sensory input to the exterior throat area outside of the thyroid cartilage. The vibrotactile sensory input is thought to vibrate the musculature and cartilages of the larynx, stimulating the mechanoreceptors in the laryngeal mucosa innervated by the superior laryngeal nerve. Afferent signals (mainly via the iSLN) are relayed to swallowing regions of the brainstem and cerebral cortex. These sensory inputs are incorporated in nucleus ambiguous and in the dorsal nucleus of vagus nerve via the ventral swallowing group and produce efferent firing of motor neuronal pools and stereotypical swallowing motor activity.

Methodology and Analyses

Participants

The present experiment recruited volunteers between the ages of 18 and 60 years old with no history of swallowing, neurological, or psychiatric problems and self-reported normal swallowing. The experiment did not include participants above age 60 in order to make certain that the results were not confounded by age effects, as swallowing and laryngeal sensory function are affected above 60 (Aviv, 1997; Aviv, et al., 1994). All of the participants used spoken English as their primary mode of communication. The study protocol was approved by the Internal Review Boards at James Madison University and Rockingham Memorial Hospital.

Power Analysis

A power analysis using Systat 13 was performed. Approximately 20 participants represented the appropriate sample number as determined by means and standard deviations from Theurer et al. (2005) and our own pilot data. Due to the expense of MRIs required for each participant and funding limitations, the study was completed with a sample size of 16 volunteers.

Table 1.

A Priori Power Analysis

Study	**Independent Variable**	**Outcome Variable**	**Expected Difference**	**Standard Deviation of Difference**	**Effect Size**	**Alpha**	**Power**	**# of subjects**
Theurer et al., 2005	Air Puff Stimuli	Swallowing Frequency	4.56	1.236	3.948	.05	0.8	3

Ludlow (pilot data)	Vibrotactile Stimuli	Swallowing Frequency	.742	.927	.8	.05	0.8	20
Ludlow (pilot data)	Air Puff Stimuli	Swallowing Frequency	.2	.637	.314	.050	.8	82

Exclusionary criteria by participant self-report during screening and again during consent:

- History of swallowing complaints or problems
- History of diagnosis and/or treatment of reflux
- Complaints of globus (sensation of a lump or mass in the throat when no mass is present)
- History of past brain injury or neurological disorders (including stroke)
- Previous neck injury
- Psychiatric disorder for which treatment was prescribed
- Speech problems
- History of epileptic seizure
- Diagnosis of progressive neurodegenerative disorders, such as: dementia, Parkinson's Disease, multiple sclerosis, peripheral neuropathy, and amyotrophic lateral sclerosis

All participants received an anatomical MRI before the study to provide 3D neuronavigation for identifying the primary somatosensory and motor regions bilaterally for functional near-infrared spectroscopy (fNIRS) recordings. Additional exclusionary criteria related to MRI and fNIRS included:

- Pregnancy
- Cardiac problems
- History of cardiac rhythm condition (including heart murmur or cardiac arrhythmia)
- Cardiac pacemaker in place
- Highly-pigmented (dark) skin color, which interferes with the measurement of light transmission through the scalp
- Presence of metal in the body that would prevent the participant from receiving an MRI

- Presence of tattoos with ferromagnetic metal or permanent makeup
- Previous occupation as a metal worker
- Broken skin on the scalp
- Claustrophobia
- Previous surgery that used surgical staples
- Artificial joints
- Not having a primary care physician

Subject Recruitment

Recruitment took place with the use a brochure, flyers, and a bulk informational email sent to JMU employees.

Telephone Screening

A telephone screening was done by the researcher or graduate students in the Laboratory of Neural Bases of Communication and Swallowing (Appendix A). Those meeting inclusion criteria were invited to come to the Laboratory to participate in the consent process.

Consent Procedure

All participants signed the informed consent form after reading through the document and before participating in the study. Researchers explained the study's procedures and answered any questions asked by the participants. Researchers also asked a group of "yes or no" questions to confirm participants' understanding of the consent form. Each participant was provided with a copy of their signed informed consent document (Appendix B). After signing the consent form, participants were asked to fill out a medical history form and the Edinburgh Handedness Inventory (Oldfield, 1971) (Appendix C). Participants were also asked to sign the following release forms:

- Release to Obtain Information (Appendix D)
- Release of Data for Educational Use (Appendix E)

- Permission for Future Contact Release Form - Laboratory of Neural Bases of Communication (Appendix F)
- Permission for Future Contact Release Form – Communication Sciences and Disorders Department (Appendix G)

Compensation

Participants were compensated for their time and efforts at the conclusion of the study, at the rate of $20 for the first hour and $10 for every hour thereafter.

Confidentiality

The confidentiality of participants was safeguarded. All participants' individual identities were kept in a locked and secure location that can only be accessed by authorized investigators. Once a participant entered the protocol, they were given a number, and further forms and data only contain the subject's identifying number. The results of this project were coded in such a way that identities will not be attached to the final form of this study. The video recordings are not available for disclosure to either the subject or others.

MRI Testing

After the consent process was completed, participants received an MRI scan at Rockingham Memorial Hospital (RMH) before returning to participate in the study. MRIs provided structural references for identifying the locations on each side of the brain to place the laser emitters and the detectors utilized with fNIRS.

Participation time

Participation took an average of 5 hours 30 minutes (range 4 hr. 40 min – 6 hr. 35 min) including the consent process, an MRI at RMH, and one to two experimental sessions. Fourteen subjects participated in both the air puff and vibrotactile stimuli conditions. Due to

equipment malfunction, two participants participated in only the air puff stimuli condition. Of those who participated in both stimuli conditions, ten participants participated in the experimental session in one visit, two participants participated in two visits on the same day separated by 1-2 hours, and two participants participated in two sessions on different days.

Equipment and Software

Magnetic Resonance Imaging (MRI)

Anatomical scans were conducted at Rockingham Memorial Hospital on a 1.5 Tesla MRI, to allow fNIRS recording from corresponding anatomy.

All other study equipment was used in the Neural Bases of Communication and Swallowing Laboratory at James Madison University.

Stimulation

Vibrotactile Stimulation

Vibrotactile stimulation was delivered via a small flat motor (size of a dime) attached to the outside of the throat over the thyroid cartilage with tape and an elastic band.

Air puff Stimulation

Air puffs were delivered via a dental device placed in the mouth with a tube aimed at the faucial pillars. The air puffs were calibrated to be a pressure of around 1 (approximately 1.43 PSI).

Other Equipment

Functional Near Infrared Spectroscopy (fNIRS)

A continuous wave functional near infrared spectroscopy (fNIRS) system (TechEn, Inc., Milford, MA, model CW6) was used. fNIRS represents a technique for measuring changes in blood oxygenation level (oxyhemoglobin) as an indirect measure of brain activity

(Irani, Platek, Bunce, Ruocco, & Chute, 2007).fNIRS is a noninvasive technology that utilizes optodes to emit laser light, similar to pulse oximetry, and measures relative changes in the concentration of oxygenated (HbO) and deoxygenated (HbR) hemoglobin. Changes of total hemoglobin can be calculated by the sum of HbO and HbR. fNIRS records wavelength amplitude changes in a region of interest, for this study over the primary motor cortex and the somatosensory cortex for oral/pharyngeal regions on both sides of the brain, during the stimulation trials. The fNIRS probe in this study consisted of two 1 x 2 x 1 probe sets (each consisting of four detectors and four laser emitters) arranged specifically and held in place in foam backed plastic, resulting in four channels of interest per hemisphere for each wavelength (690 nm & 830 nm for O2Hb). Light detectors were 3 centimeters from the laser emitters. The forward laser emitter was placed over the primary motor cortex and the back laser emitter was placed behind the primary sensory cortex. The detectors were placed over the premotor and somatosensory regions. The intensity of the laser light leaving the CW6 fNIRS machine was approximately 6 mW for the 830 nm wavelengths and around 12 mW for the 690 nm wavelengths. The intensity of the laser light actually reaching the scalp was approximately 3 mW for the 830 nm wavelengths and around 6 mW for the 690 nm wavelengths. The CW6 model has an aggregate digitizing rate of 51,200 samples per second and an output rate of 25 Hz samples per second. Live data was shown on the fNIRS computer.

The fNIRS probe (arrangement of laser emitters and detectors) was precisely placed using the Brainsight coordinates marked on the scalp after parting the hair to reduce inference from pigmentation in hair. The probe was held in place with Coban material, a self-adhesive stretching material, which was comfortably wrapped over the laser emitters and detectors and around the participant's head several times.

Table 2.

Talairach coordinates for placement of fNIRS probes

(Based on Lowell et al., 2008; Martin et al., 2004; Soros et al., 2008)

Regions	*x*	*y*	*z*	
Right Side:				
Sensory Laser emitter - A		54	-24	43
Motor Laser emitter - B		53	8	8
Detector - 2	57	-9	25	
Detector - 3	53	6	38	
Left Side:				
Sensory Laser emitter - D		-54	-24	43
Motor Laser emitter - C		-53	8	8
Detector - 5	-57	-9	25	
Detector - 6	-53	6	38	

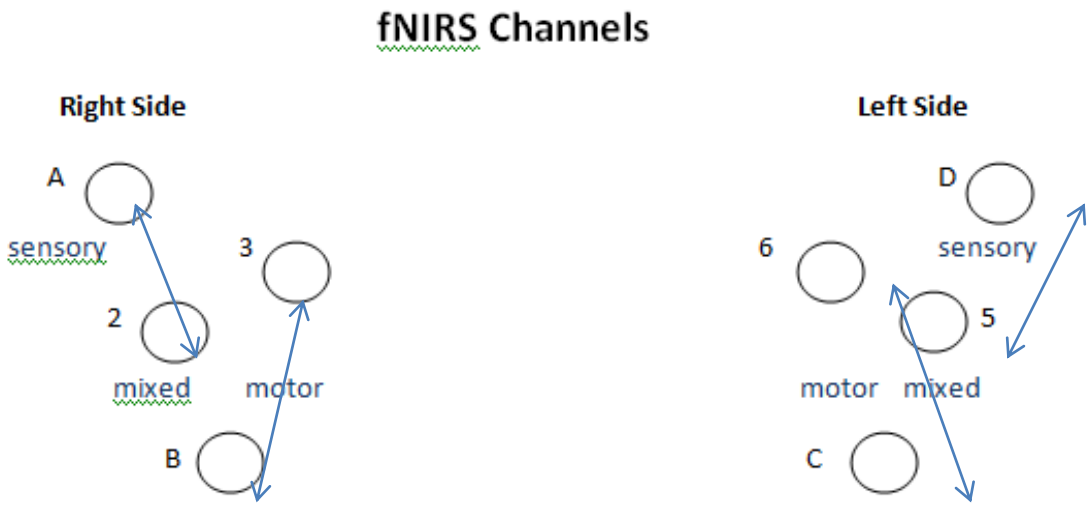

Figure 1. Arrangement of fNIRS lasers and detectors

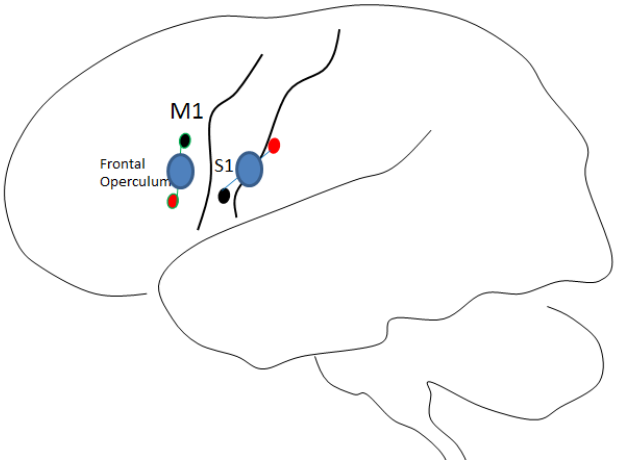

Figure 2. Location of measurement of changes in concentration of HbO in motor and sensory areas in left hemisphere

Powerlab 16 SP (*AD Instruments)*

An ADInstruments, Inc. PowerLab 16/30 (Colorado Springs, CO, model ML880) data acquisition system recorded, amplified, and digitized the output of the experiment for data analysis.

Piezoelectric accelerometer

A Kistler accelerometer (Amherst, New York, model 8778A500) is a movement transducer that was placed on the throat over the thyroid prominence, held in place with medical tape, and was used to measure swallowing movements. This is a small device, less than 1 mm by 3 mm, which weighs 0.4 gram and converts mechanical motion into an electrical signal. The voltage output reflects change in direction as the thyroid cartilage begins to elevate at the beginning of a swallow and again when the cartilage lowers at the end of the swallow. The accelerometer was connected to a Semiconductor Circuits, Inc. AC amplifier and then to Powerlab input, where the signal was recorded.

Inductotrace

The Inductotrace System (Ambulatory Monitoring, Inc., Ardsley, NY, model 10.9000), inductive plethysmography, monitored respiration and was used to identify an apneic moment to confirm the presence of a swallow (Martin, 1980; Chadha et al., 1982; Smith, 1989) It consisted of two elastic transducer bands with insulated wires. One band wrapped around the rib cage and one around the abdomen. Inductotrace measured rib cage and abdomen compartmental volume excursions through changes in inductance of the bands. The sum of these two excursion measurements was digitized in Powerlab. Abdominal, rib cage, and sum motion signals were not calibrated for volume. The amplifiers were set at 1.0 for the abdominal and rib cage signals and 2.0 for the sum signal.

Software

Brainsight

Brainsight v2.0 (Rogue Research Inc., Montreal, QC) was used to configure the MRI image to a participant's head and identify the 3-dimensional location of particular regions of the brain from the scalp position while integrating a 3-dimensional camera to the location of a pointer placed on the scalp.

ePrime software

e-Prime v2.0 (Psychology Software Tools, Inc., Sharpsburg, PA) was used in experimental design and data acquisition. The program was installed on a testing computer connected to PowerLab and ran the experimental paradigm controlling the timing of the experiment and delivering the on and off signals to each of the stimulation devices (vibrotactile and air puff stimulation).

LabChart

LabChart v7.1 (ADInstruments, Colorado Springs, CO) recorded and displayed the digitally acquired signals collected by PowerLab. The software was also used in data analysis.

HomER (Hemodynamic Evoked Response)

HomER software runs on the MATLAB platform and was used for fNIRS data analysis (T. Huppert & Boas, 2005; T. J. Huppert, Diamond, Franceschini, & Boas, 2009).

Systat 13

Systat 13 was used for statistical analyses.

Experimental Design

All subjects in this within subjects design study received air puff and vibrotactile stimuli in a random order across subjects. The independent, or within-subjects variable, was the type of stimulation (air puff or vibrotactile). The dependent variables, or outcome measures, were the frequency of swallowing and measures of changes in percent oxygenation of hemoglobin in the cortical regions being measured by fNIRS.

Experimental Procedures

Before the participant arrived, batteries were checked in all equipment, and the fNIRS machine was calibrated. Before each experiment, the investigator fit a dental

impression for each participant for holding the air puff delivery tube with 3M ESPE Express STD dental putty in an OralB Styrofoam dental tray. The impression fit the participant's upper teeth with a plastic tube (outer diameter 3/16 in) into the participant's mouth for air puff delivery towards the faucial pillars. The end of the tube in the participant's mouth had a 2- 4 inch picture wire inside (not sticking out of the tube) used to shape and aim the tube at the faucial pillars. The end of the tube in the participant's mouth had a 2- 4 inch picture wire inside (not sticking out of the tube) to aim the tube at the faucial pillars. The participant held the OralB Styrofoam dental tray in his/her mouth for approximately a minute as the putty hardened. There was no risk associated with the use of this device. No tubing or wire was re-used; and fresh putty was used for each subject.

After the participant arrived, Brainsight software was used to configure the MRI image to a participant's head and identify the 3 dimensional locations of particular regions of the brain from the scalp position of Talairach coordinates. Brainsight is a software program with a Vicon camera system with optical pointers that are used to co-reference the MRI to the patient's head using reference points of the nasion, tip of the nose, and the right and left auditory meatus. Once the co-localization was validated by the software, the scalp locations overlying particular cortical regions were marked using the optical pointer and a light-colored grease pencil or maker based on Talairach 3D coordinates. Bobby pins and clips were used to part the hair when needed (Figure 3). Bobby pins and clips were used to part the hair when needed.

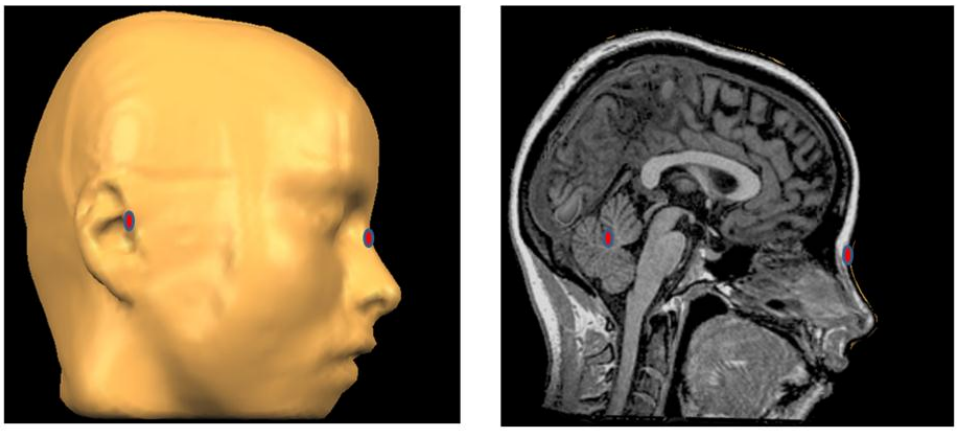

Figure 3. Co-referencing external landmarks to fit the MRI to the participants' skull

After finishing with Brainsight, subjects were seated in a dental chair. Next, the researcher attached the Kistler accelerometer and Inductotrace.

The participant was asked to insert the air puff delivery device into the mouth to allow time to acclimate to the device. The vibrotactile stimulation device was then attached to the outside of the throat with tape and an elastic band. A microphone was also clipped to the clothing of the participant. All experimental sessions were digitally video recorded. Before the experiment began, the participant inserted ear plugs to block out the sounds of vibrotactile and air puff stimulation during the experiment.

Finally, the fNIRS probe was placed over the marked coordinates and held in place with Coban material wrapped around the participant's head. The only risk to participants and the investigative team was light from the fNIRS emitters shining in a participant or experimenter's eye when the emitters were turned on. Therefore, the emitters were turned on only after they were placed and attached to a participant's scalp. The lasers were tuned off prior to moving or replacing the laser emitters on the scalp. Real-time signals were shown on the fNIRS computer. The researcher looked for a cardiac signal in the data to confirm that the detectors were picking up a clear signal. Light levels were observed during data collection

to monitor any periods of saturation which might occur. To avoid motion artifact a chin rest (using a portable, adjustable table) was placed under the participant's chin. Participants remained seated in the dental chair in the quiet dimmed room throughout the experiment.

The researchers attempted to conduct both stimulation conditions in one session and did so for 12 participants. Hence, the probe remained on the head without being moved for the two stimulation conditions for 12 out of the 16 participants. However, the use of Brainsight software enabled the researchers to place the probes over the same cortical regions with precision for the four participants who participated over two sessions.

Stimulation Presentation

The vibrotactile and air puff stimulation were presented to each participant in a random order. All subjects were intended to receive both the air puff and vibrotactile stimulation, though due to malfunctions with the vibrotactile device, two of the 16 subjects received the air puff stimulation but not the vibrotactile stimulation.

The effects of two stimulation types on swallowing frequency and the hemodynamic change in cortical regions associated with swallowing were examined. The experiment consisted of four, ten minute periods for each stimulation type, resulting in a total of eight, ten minute periods including both stimulation conditions. Presentations of the stimulation were programmed using ePrime for event marking and controlling stimulation on and off times. Each ten minute period consisted of five minutes of rest used to collect baseline data and five minutes of stimulation administered in 40 epochs of stimulation. This study was designed with a contrasting resting-state baseline interspersed with stimulation. This allows for the measurement of relative changes in the hemodynamic response due to stimulation. Both types of stimulation were presented in short trains of eight seconds with 14-30 (average of 22) seconds of inter-stimulus rest intervals. Both the air puffs to the faucial pillars and the

vibrotactile pulsations were presented in 150 millisecond pulses with 100ms off-time between pulses for three seconds, resulting in 4 Hz pulses. Participants wore both the vibrotactile and air puff devices throughout the entire experiment.

Stimulation Set-Ups

Vibrotactile

ePrime software controlled the motor of the vibrotactile device. The Serial Response Box, an e-Prime accessory, connected to the computer installed with e-Prime. An output channel of the Serial Response Box was attached to the TTL switch control box. The output from the TTL switch went to the vibrotactile control box and Powerlab. The output from the vibrotactile control box went directly to the vibrotactile device.

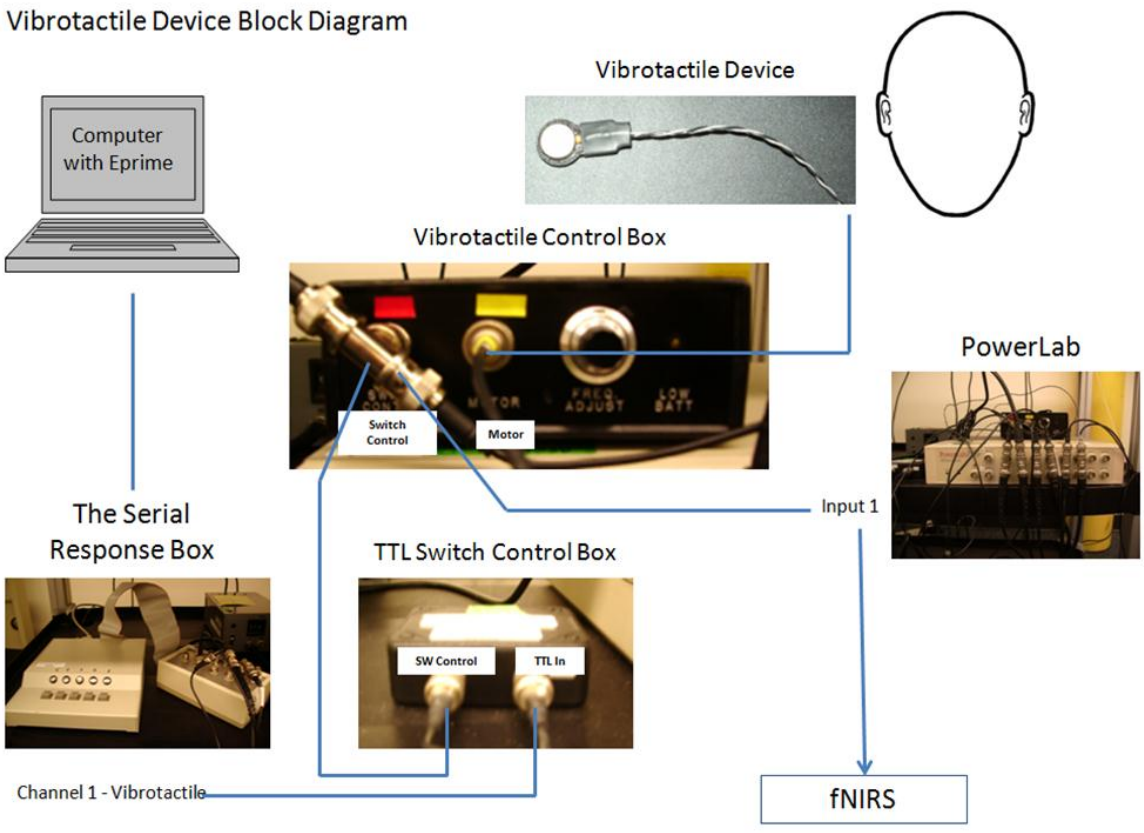

Figure 4. Vibrotactile stimulation equipment

Air puff

Air exited a breathing air tank and went through two regulators. The first regulator reduced pressure coming out of the tank to 60 PSI. The second regulator then conditioned the air pressure down to 10 PSI. The tubing coming out of the regulator split and one end went to the digital manometer, which read the pressure of the tube going to the valve in PSI. The other end went to the valve that was controlled by ePrime. After the air went through the two-way on/off valve, it splits and went to the 1) relief valve (bottle) and 2) to the participant and the Valydine pressure transducer model DP 45-30, which turned the air pressure received by the patient into a voltage signal that could be read on the Validyne pressure meter model CD 379. The pressure reading on the Valydine pressure meter was equivalent to the pressure going to the participant.

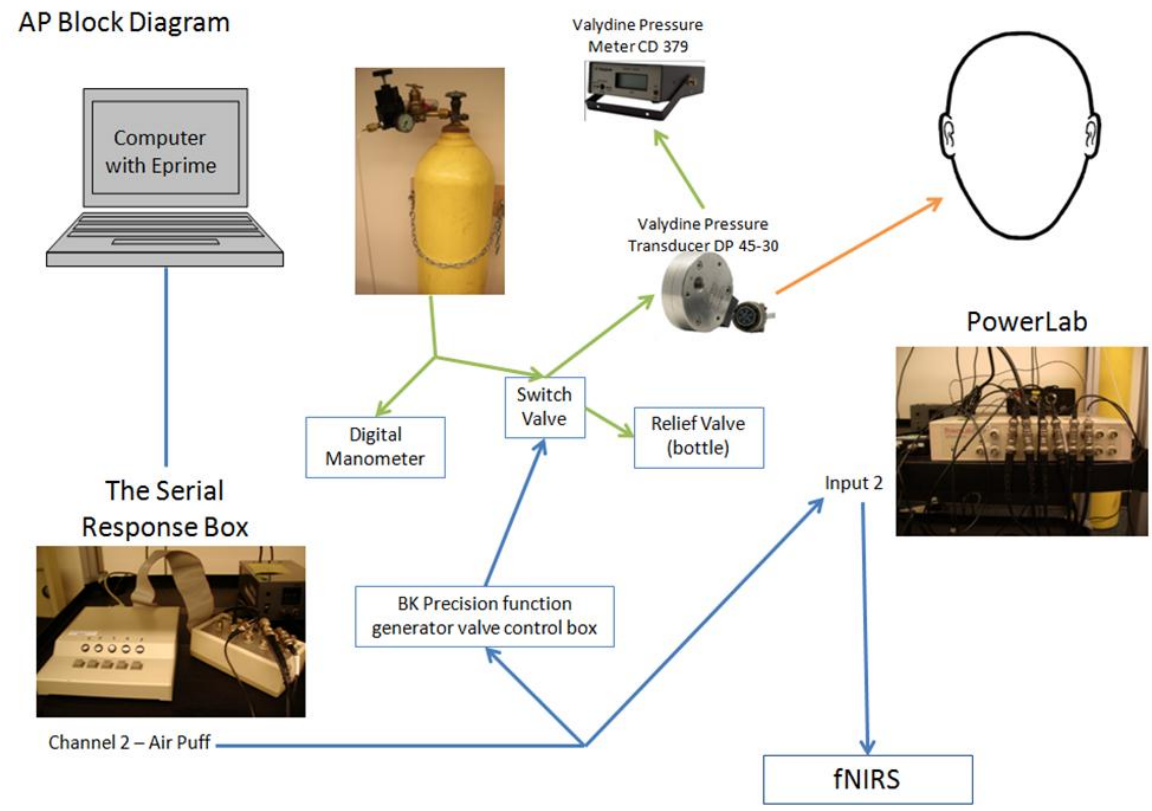

Figure 5. Air puff stimulation equipment

Risks and Discomforts

MRI Scans

Individuals with any implanted metal objects in the brain or body are at risk of injury with MRI procedures due to the high magnetic force to which they are exposed. Therefore, individuals with one or more of the MRI exclusion criteria were excluded from the study. The principal investigator reviewed each of the exclusion criteria with the participant. Acoustic noise is generated in the magnet when the gradient coils are energized and de-energized in the magnetic fields to create MRI images. The main discomfort associated with the study was the need for the subject to remain quiet within the scanner for the duration of testing, about 20 minutes maximum.

Air Puff Stimulation and Vibrotactile Stimulation

The air puff stimulation and vibrotactile stimulation are both non-invasive forms of stimulation and carry no known risks. The air puff delivery system involved wearing a device similar to a retainer or mouth guard. The vibrotactile device was attached to the neck with tape, which could cause brief skin irritation after tape removal.

Piezoelectric accelerometer and Inductotrace

The piezoelectric accelerometer and Inductotrace are both non-invasive and carry no known risks. The accelerometer was attached to the neck with tape, which could cause brief skin irritation after removal. The Inductotrace bands were wrapped around the participant's rib cage and abdomen during the experiment but do not cause any discomfort, as they stretch with the breathing movements.

fNIRS

There was a risk of lasers being shined into to the eyes. However, the lasers used are similar to a laser pointer, and the risk was minimal. Also, markers were used on the scalp during probe during placement of the fNIRS sensors. These marks washed away, and no hair was removed. Additionally, the sensors were slightly uncomfortable on the scalp as they are held in place with light pressure.

Outcome Measurements

One outcome measure was the frequency of swallows per minute occurring during the stimulation periods. The total number of swallows between each of the stimulated and non-stimulated conditions for each device were compared.

The second outcome measure was the percent change in blood oxygenation level of oxygenated and deoxygenated hemoglobin during the stimulation and non-stimulation periods by device. Continuous recording of reflected light to the detectors was used to derive changes in oxygenated (HbO) hemoglobin over the 40 air puffs or vibrotactile pulses.

Data Analysis Procedures

Swallowing Frequency Analysis Procedures

Swallowing was identified via respiratory monitoring and an accelerometer device placed on the throat indicating laryngeal movements. Both were attached to Powerlab, and the data from both could be viewed in LabChart. Inductotrace was used to monitor respiration and identify instances of respiratory apnea which occur in the middle of each swallow. The laryngeal movement pattern of a swallow onset and offset using a piezoelectric accelerometer also confirmed the presence of a swallow. Laryngeal and respiratory movements were continually recorded throughout the experiment via PowerLab. Any questionable swallows were not included in the data analysis.

Marking Swallows Procedures

Swallows were marked with the comment "swallow onset" in the LabChart data files for each participant during the periods of no stimulation for the vibrotactile and air puff conditions. The swallow pattern was identified through extensive review of LabChart files that included recorded reliable swallows marked before the experiment began for most participants using a pulse generator. The criteria for a swallow included the aforementioned swallow pattern that occurred on exhalation and included an apneic moment in respiration. as seen in the "Sum" Inductotrace signal. The phase of respiration in which a swallow occurred was determined using a channel in LabChart that displayed the first derivative of the "Sum" Inductotrace signal (999 point window width). In the "Sum 1st Derivative" channel, a line was drawn at zero. A swallow occurring when the "Sum 1st Derivative" signal was below zero was considered to occur during exhalation. After marking all swallows, the comments were exported to an Excel spreadsheet. Swallows were counted for each 40 minute stimulation condition (including the time of rest with no stimulation) and the swallowing frequency per minute was calculated.

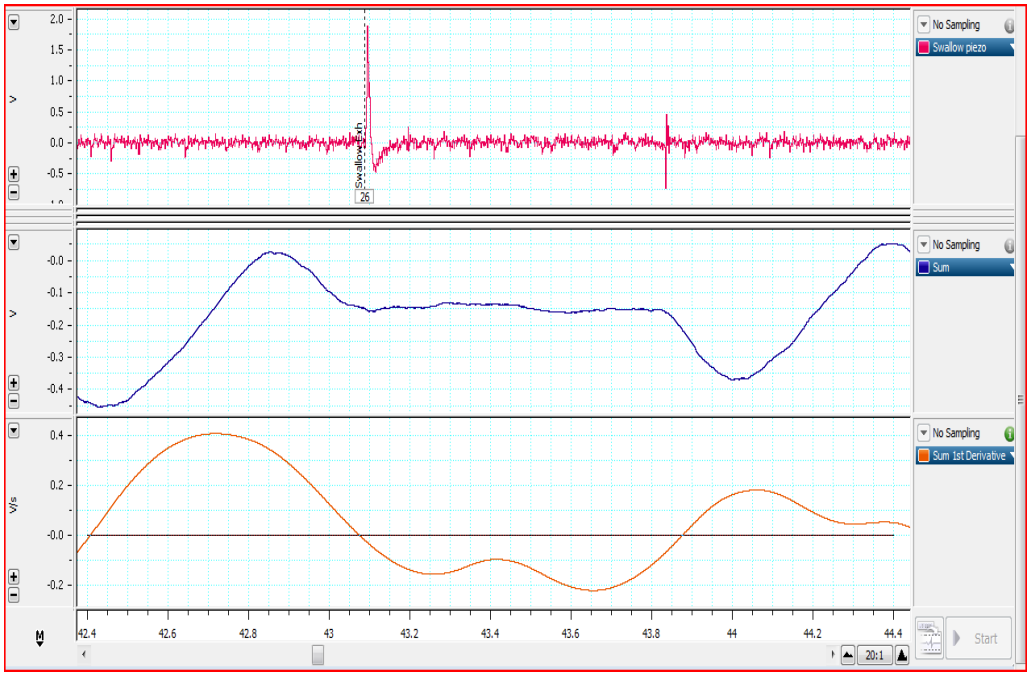

Figure 6. Example of a marked swallow in Chart. The swallow pattern recorded by accelerometer is shown in the top channel. The apneic moment is seen in the middle channel. The Sum of the 1st Derivative is shown in the bottom channel.

Intra-rater Reliability

Following data collection and analysis of the 16 participants, intra-rater reliability in identifying and marking swallows was assessed. Data from the 16 participants yielded 30 files that could be used for assessing intra-rater reliability; 25% were randomly chosen and the files were copied and renamed. Swallows were then re-marked for each blinded file and then compared to the originally marked files for consistency and accuracy.

Swallowing Frequency Statistical Analysis

To assess the relative effects of vibrotactile versus air puff stimulation on swallowing frequency, swallowing frequency was assessed for each stimulus time-block and each condition, and means were generated across time blocks per subject and then for each condition within subjects. Group means were assessed with repeated measures ANOVAs to determine if the two stimulation conditions differed from the baseline swallowing frequency and if there were differences between stimulation conditions.

fNIRS Analysis Procedures

Near-infrared spectroscopy data files were opened and analyzed in HomER data analysis software (Huppert & Boas, 2005). After a file was opened in HomER, all channels were assessed in an unfiltered view for a cardiac signal and appropriate signal intensity. A cardiac signal was indicative that the channel recorded had a good signal and that there had been good contact between the laser and detector and the participant's scalp. Channels that did not contain a cardiac signal were not included for processing, A low-pass filter (.5 Hz) and high-pass filter (.016 Hz) were then applied in order to reduce respiration and cardiac components of the signals, since the hemodynamic response of interest is relatively slow in

comparison to the other physiological signals. The "Cov. Reduced dConc" filtering was then applied (a third principle component analysis performed on the concentration data) for data processing.

The periods that represented the least motion artifact after filtering were identified and epochs during this time were chosen for event-related averaging. Forty stimulation or control (no stimulation) epochs were included in the event-related averages. The epoch times were identified in LabChart and manually entered into HomER. The stimulation epochs and non-stimulation epochs, controlled via E-Prime, were included as auxiliary channels in the fNIRS machine and were recorded in HomER. Swallows were identified in the LabChart data files and manually entered in HomER. The average was then performed over 25 seconds for epochs in each condition (no stimulation, air puff, or vibrotactile), from five seconds before the start of an epoch to 20 seconds following the initiation time of each epoch. Averaged data were then exported to an Excel spreadsheet. The peak hemodynamic response was expected four – six seconds after the onset of swallowing or stimulation onset (Figure 7, 8). The mean change in concentration in HbO (in arbitrary units), multiplied by 10^6 at five seconds after the start of each marked swallow, was computed for each subject during air puff and vibrotactile stimulation and during control periods.

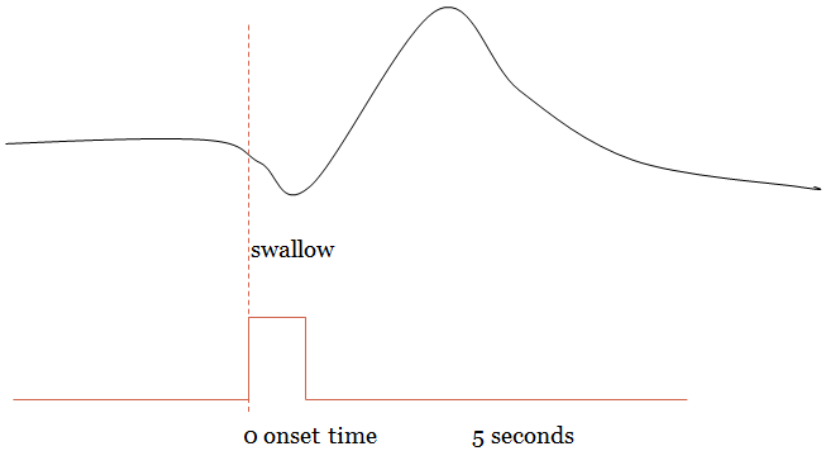

Figure 7. Model of expected hemodynamic response to swallows

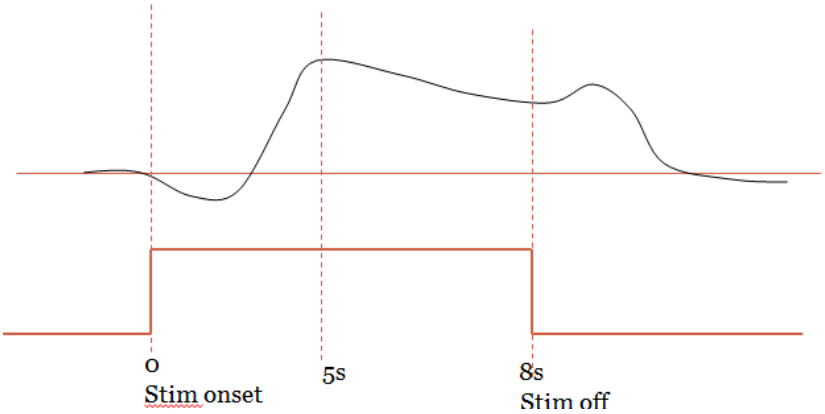

Figure 8. Model of the expected hemodynamic response to stimulation

Results

Participants

The experiment included 16 healthy adult volunteers between the ages of 28 and 60 years of age, mean 46 years 11 months, with no reported history of swallowing, neurological, or psychiatric problems and self-reported normal swallowing. Seven were male, nine were female. Seventeen people met the inclusion criteria and were consented. One participant turned 61 before the next available MRI appointment and had to be excluded. As Wassenaar and Van den Brand (2005) found that the higher levels of melanin interfered with the reflected wavelength transmission in near-infrared spectroscopy measurements, all participants had light skin color.

The air puff condition was run on all 16 participants. Due to malfunction of the vibrotactile device, that condition was run on 14 of the 16 participants. Twelve subjects participated in the vibrotactile and air puff conditions in the same sitting while .two subjects participated in the two stimulation conditions over two sessions in the same day with a two hour break between the two sessions. The same Brainsight markings on the scalp were used for laser emitter and detector placement for both sessions. The two remaining subjects participated in the two conditions on different days with the Brainsight markings done on each day.

Data Loss

Researchers were unable to identify swallows in the vibrotactile condition for Participant 101 due to noise interfering with the accelerometer signal. Inductive plethysmography (Inductotrace) malfunction in Participant 105 resulted in no swallowing frequency data available for that participant.

As the chin rest obstructed the investigators view of the larynx, the investigators were unable to see whether or not the subject swallowed as was originally planned. Instead, initially participants were asked to push the button on the pulse generator to "mark" swallows when they swallowed. The LabChart recordings of the marked swallows were used a reference showing the accelerometer movement pattern and inductive plethysmography during a swallow for identifying swallows during the experiment.

Intra-rater Reliability

Re-identification and marking of swallows was performed to assess intra-rater reliability. Data from the 16 participants yielded 28 files that could be used for assessing intra-rater reliability; 25% (7 files) were randomly chosen and blinded. Swallows were then re-marked for each blinded file and then compared to the originally marked files for consistency and accuracy. Of the total number of 20 minute recordings that were reviewed twice, 611 of the 650 swallows were in agreement resulting in an overall 94% percent agreement.

Swallowing Frequency

The number of swallows occurring in the 20 minute intervals was measured for each of the 4 conditions: vibrotactile stimulation and the corresponding control period and air puff stimulation and the control period.

Repeated measures analyses were conducted to examine changes in swallowing frequency with stimulation. A statistically significant within subject change was shown for stimulation compared to control, $F(1, 11) = 18.579$, $p = .001$, indicating the frequency of swallowing was greater during stimulation periods than during non-stimulus periods. There was a significant difference in stimulation type, $F(1, 11) = 10.749$, $p = .007$, although the interaction between stimulation type and the stimulation versus no stimulation was not

statistically significant, $F(1, 11) = 3.35$, $p=0.095$. To examine each stimulation effect, post hoc paired t-tests were computed between stimulation and no stimulation periods for each stimulation type separately. A statistically significant change in the number of swallows was found between air puff stimulation and the corresponding no stimulation condition, $t(15) = 3.4378$ $p = .004$(Figure 9), while no difference was found in the number of swallows between the vibrotactile stimulation period and the control period, $t(11) = .763$, $p = .461$(Figure 10). The number of swallows was higher for 13 of the 16 participants during the air puff stimulation period compared to that with no stimulation.

Table 3.

Mean Number of Swallows by Condition

Condition	Number of Participants	Mean Number of Swallows	
		Control	Stimulation
Air Puff	16	15.812	24.562
Vibrotactile	12	16.250	18.417

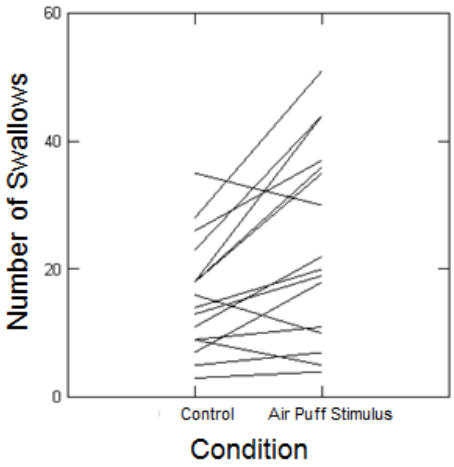

Figure 9. Mean number of swallows during 20 minutes with air puff stimulation and the corresponding 20 minutes of no stimulation condition. Each line shows the control and air puff stimulation values for an individual subject (*N*= 16).

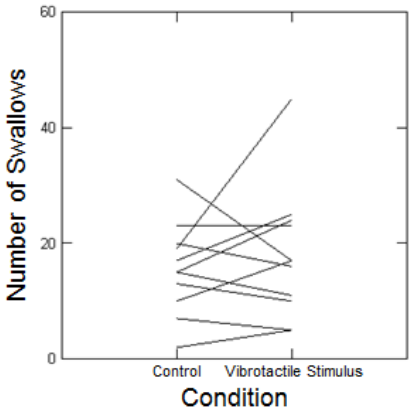

Figure 10. Mean number of swallows during 20 minute vibrotactile stimulation and corresponding 20 minute no stimulation condition. Each line shows the control and air puff stimulation values for an individual subject (*N*=12).

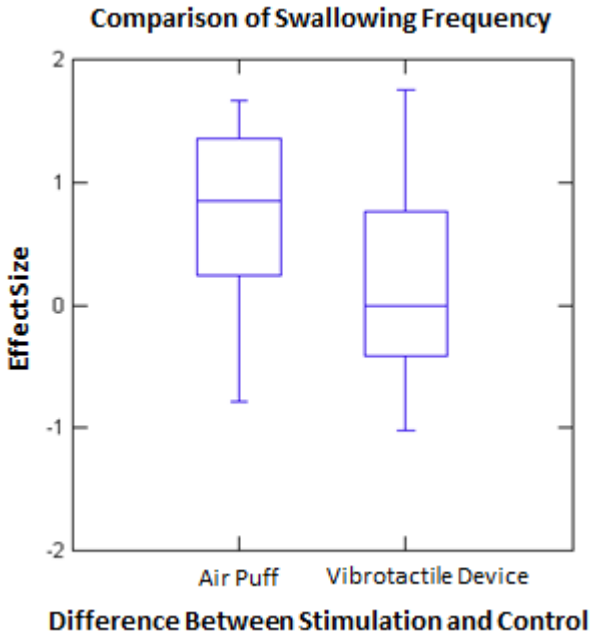

Figure 11. Comparison of effect size between stimulation and control (equals change in number of swallows during the stimulation condition from the no stimulation condition divided by mean standard deviation for conditions). The mean effect size was computed separately for the air puff and vibrotactile conditions

Functional near-infrared spectroscopy (fNIRS)

fNIRS data during swallows

For each subject the mean change in concentration in HbO (in arbitrary units) multiplied by 10^6 at 5 seconds after the start of each marked swallow was computed for each subject during air puff and vibrotactile stimulation and during control periods. Post hoc one-sample t-tests were computed to compare the effects by region and by side. Effects were considered statistically significant at the .05 significance level. A statistically significant change in the concentration of HbO was found between the swallows during stimulation and control periods without swallows in the sensory region on the right side, $t(6) = 3.22$ $p = .018$, indicating an increase in HbO for swallow versus control. A non-significant trend was noted in the left motor region, $t(5) = 1.649$, $p = .160$. No difference was found between the swallows during stimulation and control periods without swallows in the motor region on the right, $t(6) = .763$, $p = .889$, or in the sensory region on the left, $t(8) = -.772$, $p = .463$. The fNIRS data suggests that cortical activation for swallowing occurs in primarily the right sensory region but also on the left side in the motor area (Figure 12, 13)

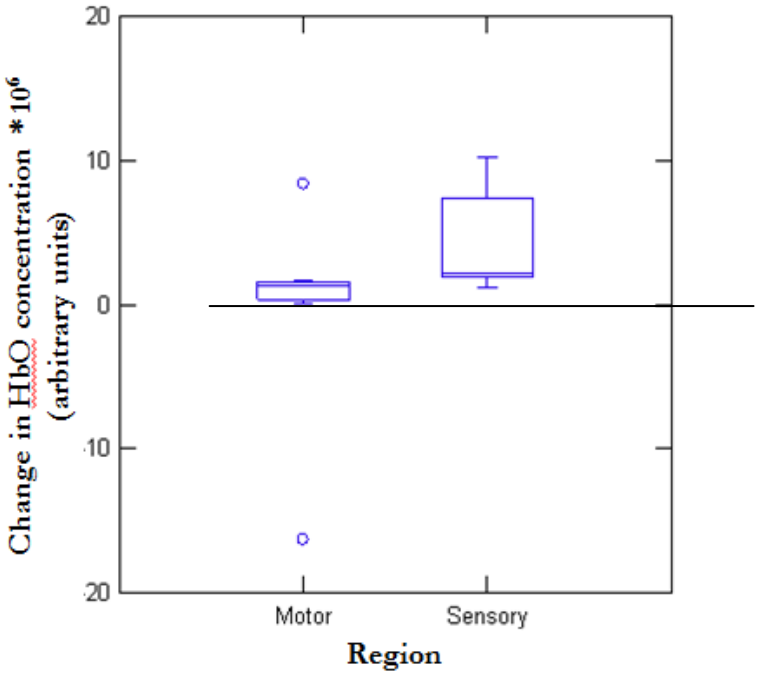

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Figure12. Comparison of change in HbO concentration between motor and sensory regions on the right side

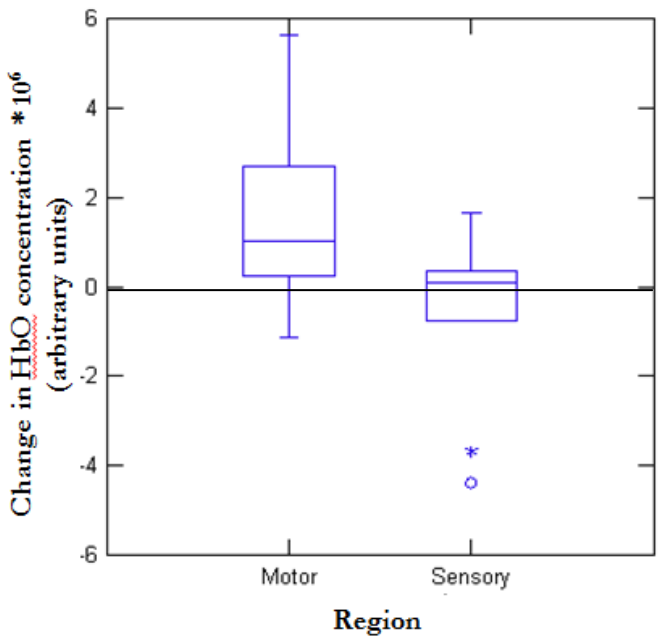


Figure 13. Comparison of change in HbO concentration between motor and sensory regions on the left side.

fNIRS data during air puff and vibrotactile stimulation

fNIRS event-related changes in oxyhemoglobin (HbO) concentration data was collected for 16 participants. For some participants, only partial fNIRS data was collected, as some channels were too noisy to yield useful results. A total of 84 channels were recorded from 14 participants during the vibrotactile condition. Of which, 23 did not contain a cardiac signal and were deemed too noisy resulting in 61 channels remaining. A total of 96 channels were recorded from 16 participants during the air puff condition. Of which, 25 did not contain a cardiac signal and were deemed too noisy resulting in 71 channels remaining.

For each subject the mean change in concentration in HbO (in arbitrary units) multiplied by 10^6 at 5 seconds after the start of stimulation was computed for each subject during air puff stimulation, the control for air puff, for vibrotactile stimulation and the control for vibrotactile stimulation. A two-way repeated ANOVA was computed to compare the effects of air puff versus vibrotactile on stimulation and control conditions by side and

by region. Main effects were considered statistically significant at the .05 significance level. A significant main effect of type of stimulation (air puff versus vibrotactile), $F(1, 33) = 19.491$, $p \leq .0005$, indicated that the two stimuli differed in the effects on changes in blood oxygenation in the brain. The change in HbO decreased with air puff stimulation versus the control condition while no change in HbO occurred with the vibrotactile stimulation compared to the control condition (Figure 14, 15).

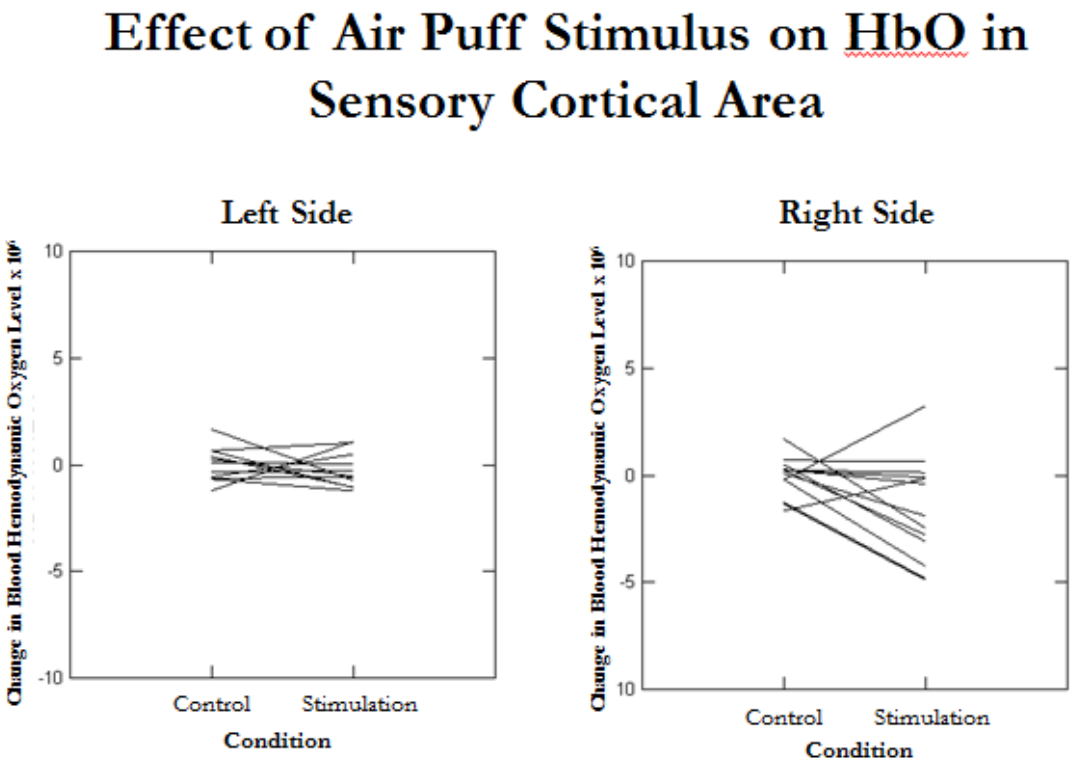


Figure 14. Effect of air puff stimulus on HbO in sensory cortical area. Each line shows the change in blood oxygen concentration * 10^6 for control and air puff conditions for each individual subject in the sensory cortical area (Left side, $n = 10$, Right side, $n = 12$). Blood oxygenation level (HbO level * 10^6) remained about the same on the left side and decreased on the right side with air puff stimulus compared to the control condition in all but 2 of 12 subjects.

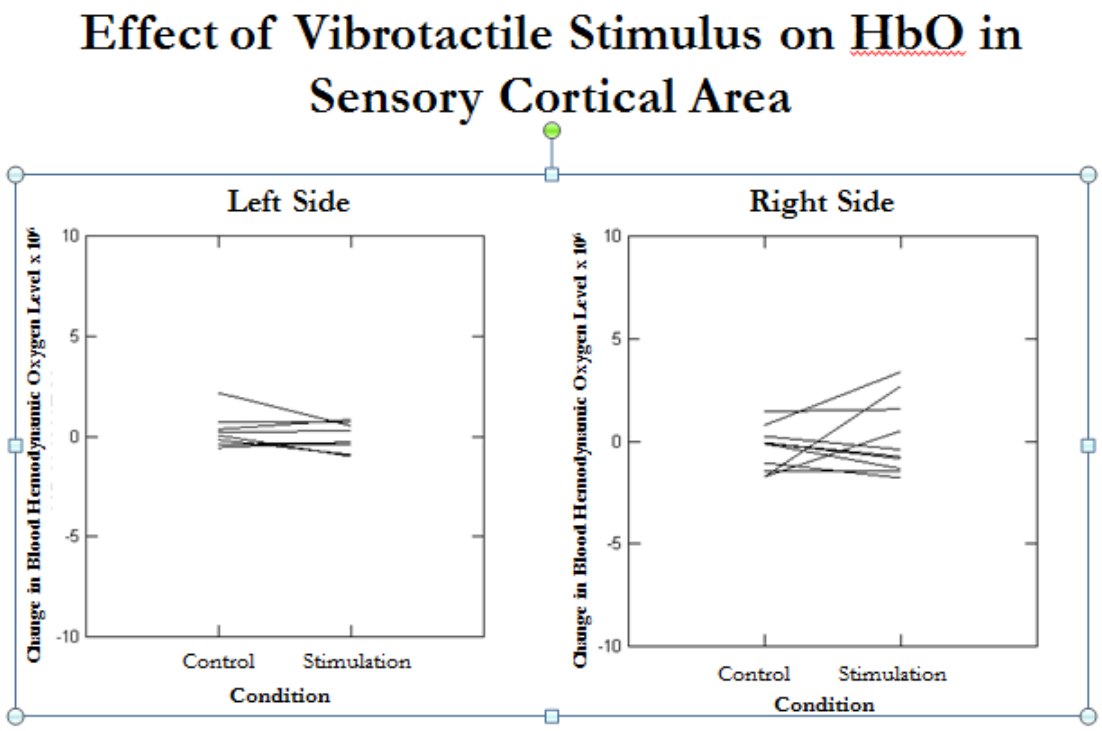


Figure 15. Effect of vibrotactile stimulus on HbO in sensory cortical area. Each line shows the change in blood oxygen concentration * 10^6 for control and vibrotactile conditions for each individual subject in the sensory cortical area (Left side, $n = 8$, Right side, $n = 9$). The decrease in HbO on the right side seen with the air puff stimulation is not seen with the vibrotactile stimulation.

No significant interactions were found between type of stimulation and the side of the brain, $F(1, 33) = .666$, $p = .420$; type of stimulation and region of the brain, $F(1, 33) = 1.629$, $p = .211$; or type of stimulation, side, and region of the brain, $F(2, 33) = 2.087$, $p = .140$. No significant main effect of the stimulation versus control conditions was found, $F(1, 33) = .464$, $p = .501$, indicating no overall difference between the change in blood concentration HbO level * 10^6 in the stimulation and control conditions. A significant interaction effect of the stimulation versus control conditions and the side of the brain, $F(1,33) = .4.326$, $p = .045$, but no significant interaction effect of the stimulation versus control conditions and the region of the brain occurred $F(2,33)=.805$, $p = .465$. A significant 3 way interaction between stimulation versus control conditions, side, and region of the

brain occurred $F(2,33) = 4.829$, $p = .014$ and a significant 4 way interaction between air puff verses vibrotactile stimulation by stimulation versus control conditions by side and by region of the brain $F(2,33)=3.282$, $p = .050$.

Because there were significant region and site interactions, 2 way repeated ANOVAs were computed separately for each side by region combination comparing the effects of air puff versus vibrotactile stimulation and the stimulation versus control conditions to determine how the change in blood concentration HbO level (multiplied by 10^6) between stimulation type and stimulation versus no stimulation within each side by region (sensory versus motor). No statistically significant change ($p = 0.05/4 =\leq 0.0125$) in HbO concentration was found between air puff and vibrotactile stimulation on either side in the sensory or motor regions. A non-significant trend was found in the change in HbO concentration between air puff and vibrotactile stimulation on the left side in the motor region $F(1, 5) = 8.893$, $p = .031$ (Figure 16)

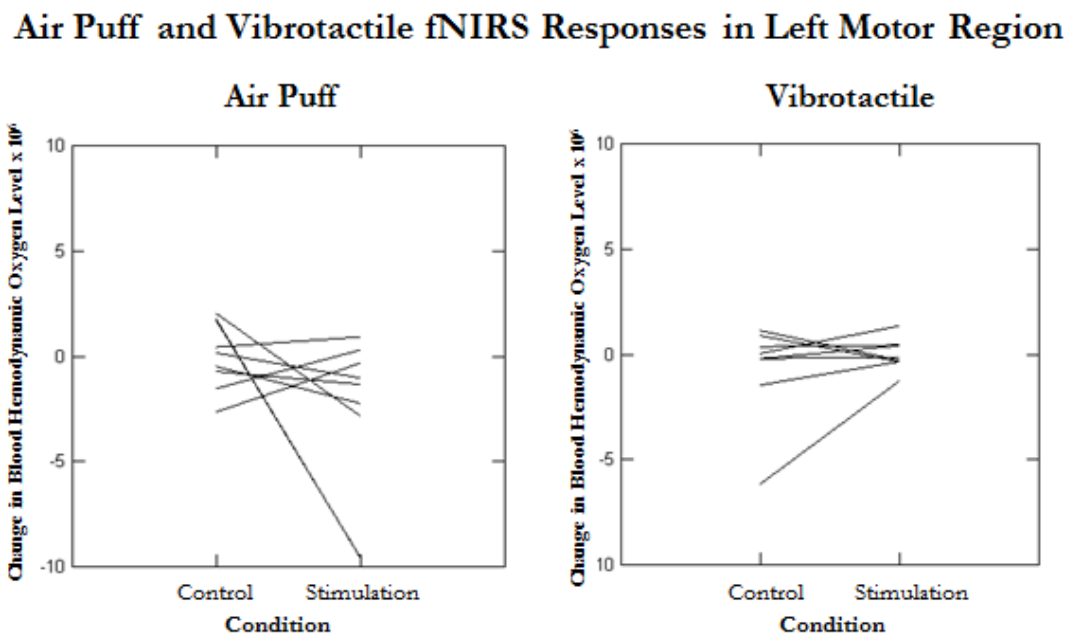
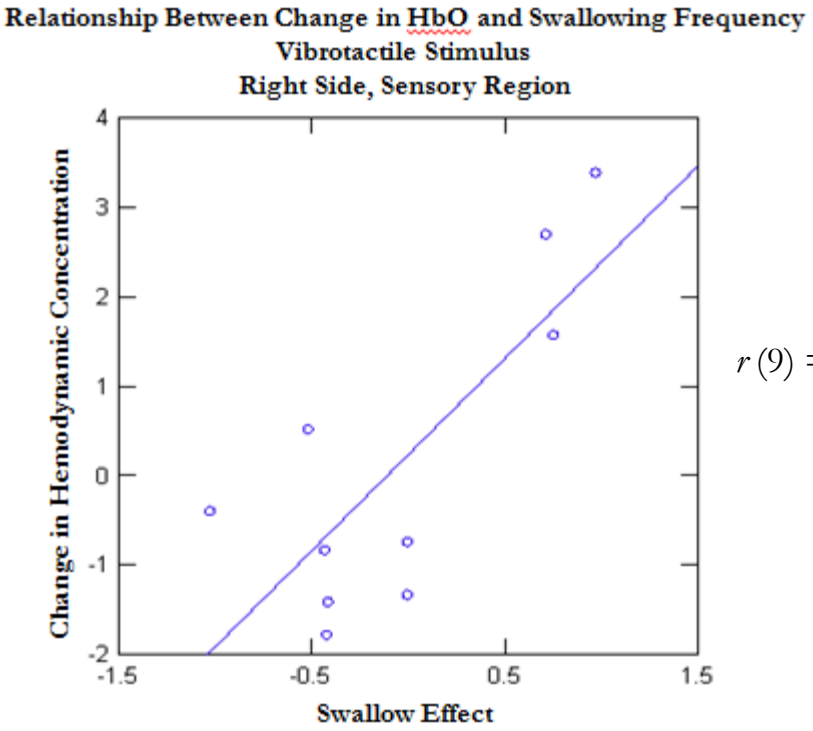


Figure 16. Air puff and vibrotactile fNIRS responses in left motor region. Each line shows the change in blood oxygen concentration * 10^6 for control and stimulus conditions for each individual subject in the motor cortical area (Air Puff, n = 8, Vibrotactile, n = 8). Primarily, an increase in HbO is seen with vibrotactile stimulation and not seen with the air puff condition.

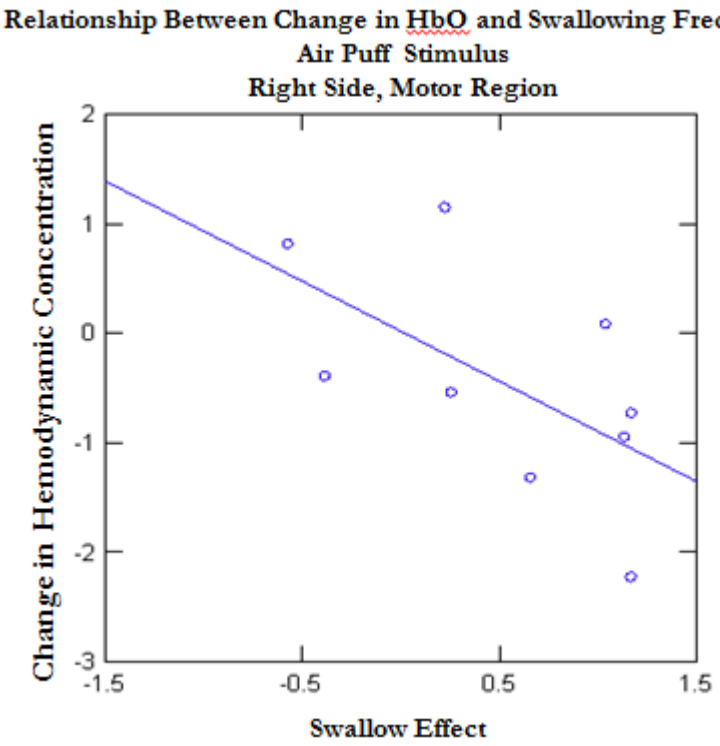
Relationships between change in swallowing frequency and change in HbO concentration

The relationship between the change in swallowing frequency with stimulation (using the individual effect sizes with stimulation from no stimulation and the change in HbO concentration at 5 seconds) were computed separately for the vibrotactile and the air puff conditions by computing Pearson Correlation Coefficients and using a Bonferroni corrected p value to indicate a significant difference at (p <.0125). A positive correlation was found between the swallow frequency effect size and the change in hemoglobin oxygenation with the vibrotactile stimulation in the right sensory region, $r(9) = .777$, $p = .008$. A negative trend was noted for the air puff stimulation in the right motor region, $r(9) = -.626$, $p = .053$. Correlations of changes in swallowing were not found with the fNIRS response to vibrotactile stimulation in the right motor region, $r(4) = -.656$, $p = .236$; the left sensory region, $r(8) = .063$, $p = .872$; or the left motor region, $r(7) = .278$, $p = .505$. No significant correlations were found between changes in swallowing to the fNIRS response to air puff stimulation in the right sensory region, $r(12) = -.377$, $p = .205$; the left sensory region, $r(10) = -.207$, $p = .541$; or the left motor region, $r(8) = -.213$, $p = .582$.



$r\,(9) = .777, p = .008$

Figure 17. Relationship between change in HbO and swallowing frequency with vibrotactile stimulus on the right side in the sensory region Positive relationship between an increase in HbO concentration on right side, in sensory region, with an increase in swallowing frequency with vibrotactile stimulation ($n = 10$)



$r\,(9) = -.626, p = .053$

Figure 18. Relationship between change in HbO and swallowing frequency with air puff stimulus on the right side in the motor region. Inverse relationship between a decrease in HbO concentration on the right side, in the motor region, with an increase in swallowing frequency with air puff stimulation ($n = 10$)

Discussion

Swallowing Frequency

The current study sought to evaluate the effect of two stimulation devices on swallowing. As hypothesized, participants had increased frequency of swallowing during stimulation periods compared to the non-stimulus periods. The finding that air puff stimulation to the oropharynx (glossopharyngeal nerve) evoked an increase in swallowing in healthy adults is consistent with the literature (Theurer, et al., 2005; Theurer, et al., 2009). Contrary to what was hypothesized, participants' frequency of swallowing with the vibrotactile stimulation was not equal the frequency of swallowing in the air puff condition. In fact, there was no significant change in the frequency of swallowing during the vibrotactile stimulation compared to no stimulation.

The mechanism by which air puff stimulation most likely invokes swallowing is thought to involve activation of the brainstem central pattern generator for swallowing. The air puff stimulation activates mechanoreceptors in the mucosa in the faucial pillars, innervated by afferents in the glossopharyngeal nerve. The afferents relay to nuclei in the nucleus tractus solitarius via interneurons in the reticular region to the ventral swallowing region in the brainstem containing the central pattern generator for the pharyngeal component of swallowing. As mentioned earlier, electrical stimulation of the pharyngeal branch of the glossopharyngeal nerve or the internal superior laryngeal nerve (30–50 Hz) in animals induces swallowing (Kitagawa, 2002; Sinclair, 1971; Doty, 1951; Miller, 1971b). Thermal stimulation of glossopharyngeal nerve has been shown to upregulate swallowing in anesthetized cats. (Chi-Fishman, et al., 1994) and air puff stimulation could also excite thermoreceptors in addition to mechanoreceptors depending on the temperature of the air (Theurer, et al., 2005). As salivation was not controlled or measured in this study, the

potential influence of increases in salivation secondary to air puff stimulation may have contributed to an increased swallowing rate to clear greater volumes of saliva. Theurer et al. suggested this possibility be ruled out in future studies (2005).

Given that stimulation of the internal superior laryngeal nerves has been shown to evoke swallowing in the medulla in decerebrate and anesthetized animals (Doty, 1951; Kitagawa, et al., 2002; Miller, 1972b; H. Pommerenke et al., 2002; W. T. Pommerenke, 1927; Sinclair, 1971; Sumi, 1977; Takagi, et al., 2002) we expected increased swallowing with sensory input from the vibrotactile device to the internal superior laryngeal nerve. One likely explanation was the lack of adequacy of the motor for providing adequate vibration to penetrate the laryngeal tissue to stimulate the tissues innervated by the superior laryngeal nerve inside the larynx. The pancake motor used was small and in participants with a large fat layer the motor may have not been adequate in vibration amplitude. In addition, although Coban was wrapped to maintain the motor in place on the throat over the thyroid cartilage, this may have not provided an adequate pressure of the motor to vibrate the thyroid cartilage. Participants had differing amounts of muscle and fat in their neck which was not controlled for. The vibrotactile device was attached with tape and the participants' necks were loosely wrapped with self-adhesive stretching material to ensure the vibrotactile device stayed in place, additional pressure or stronger vibrations may be required to have the vibration penetrate deeper to the laryngeal tissues to stimulate the tissues inside the larynx with mechanoreceptors innervated by the internal branch of the superior laryngeal branch. Further, the vibrotactile device was set to produce short trains of bursts of vibration at 4 Hz over 8 seconds. Perhaps continuous stimulation rather than pulsed stimulation would have been more effective evoking swallowing. These factors are now being evaluated in an ongoing study.

Functional near-infrared spectroscopy (fNIRS)

The current study also sought to evaluate the effects of the two types of stimulation in the cortical regions involved in sensory-motor control. First, to determine if the fNIRS recordings were sensitive to HbO changes during swallowing we examined whether there were changes when all of the swallowing events were identified and averaged across the two recordings. An increase in HbO was found in the right sensory region at 5 s after the onset of swallowing and a similar non-significant trend was found in the left motor region. These findings suggested that cortical activation for swallowing occurred in primarily the right sensory region but also on the left side in the motor area.

Effects of air puff and vibrotactile stimulation on hemoglobin oxygenation

Overall there was a significant difference in the effects of air puff versus vibrotactile stimulation which interacted with stimulation versus control, side (left and right) and region (motor and sensory). Post hoc analyses found a trend for a significant difference in the left motor region and a significant interaction of the air puff versus vibrotactile interaction with stimulation versus control in the right sensory region indicating that the effects of the two different types of stimulation differed in the right sensory region.

Air puff stimulation

One of the more significant findings to emerge from this study was that the two stimuli differed in the effects on blood oxygenation changes in the brain. Surprisingly, the change in blood concentration HbO level * 10^6 decreased with air puff stimulus compared to the control condition. While fMRI demonstrated significant change in hemoglobin deoxygenation in the Soros (2008)and Lowell (2008) studies, with the use of fNIRS we were

able to examine changes in hemoglobin oxygenation which showed a reduction in hemoglobin oxygenation demonstrating an active cortical suppression with air puff stimulation.

These findings add to the growing body of literature on a negative Blood Oxygenation Level Dependent (BOLD) response to sensory stimulation. A typical oxygenation response consists of an increase in oxyhemoglobin and a decrease in deoxyhemoglobin concentration changes. The inverse oxygenation response is characterized by a decrease in change in oxyhemoglobin and an increase in deoxyhemoglobin (Sato et al., 2005; Strangman, Culver, Thompson, & Boas, 2002; Wenzel et al., 2000). There is a significant correlation between BOLD measures, used in MRI studies, and HbO measures, used in the current fNIRS study (Strangman et al., 2002). Most fMRI studies describe positive BOLD response, but several fMRI and fNIRS studies have reported a negative signal response similar in time to the positive BOLD response with respect to the onset, the rising edge, and the time to peak deoxyhemoglobin (Holper, Shalom, Wolf, & Sigman, 2011; Strangman, et al., 2002; Wenzel, et al., 2000). Wenzel et al. used fNIRS to measure changes in oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentration in the occipital cortex in response to visual stimulation and found a decrease in HbO concentration and a rise in deoxyhemoglobin. fNIRS and fMRI studies have found negative BOLD responses during motor imagery tasks in the primary motor cortex (Gazzola & Keysers, 2009) the somatosensory cortex (post-central gyrus) (Amedi, Malach, & Pascual-Leone, 2005) secondary motor areas (Holper, et al., 2011) and visual areas (Kaas, Weigelt, Roebroeck, Kohler, & Muckli, 2010). When the source and detector are positioned as to maximize the measured signal as was done in the current study, the partial- volume effect is minimized and the results are thought to be accurate (Boas & Dunn, 2010).There are several physiological

explanations for inverse oxygenation responses but it may represent a cortical inhibition response to the air puff stimulation in contrast with the active increase in HbO during swallowing. A negative BOLD response is correlated with decreases in cerebral blood flow with reduced oxygen consumption primarily due to neural inhibition (Holper, et al., 2011; Shmuel et al., 2002). However we did see opposing responses to vibrotactile stimulation in adjacent areas (Figure 19).

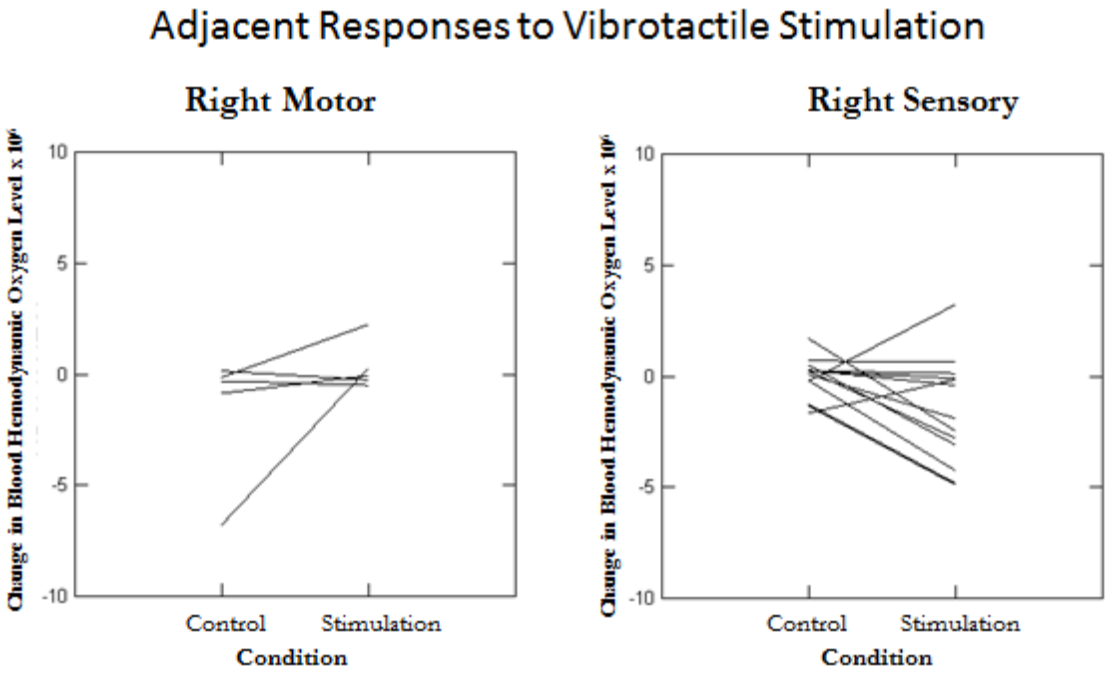


Figure 19. Adjacent responses to vibrotactile stimulation in the right hemisphere. Each line shows the change in blood oxygen concentration * 10^6 for control and vibrotactile conditions on the right side for an individual subject (Right Motor, n = 5, Right Sensory, n = 12) Blood oxygenation level increased with stimulation compared to the control condition in the right motor region and decreased in the left motor region.

Inhibition could be interpreted as "suppression processes triggered by adjacent brain regions which may deactivate sensory inputs that could potentially disrupt or interfere with the required goal of a given task" (Holper, et al., 2011). The suppression response to the air puff stimulation in comparison with the excitatory response during swallowing suggests that

the air puff stimulation might serve to produce cortical inhibition and differ from excitation at the brainstem resulting in increased swallowing.

Vibrotactile stimulation

Contrary to expectations, vibrotactile stimulation did not cause an overall change in hemoglobin oxygenation in the cortical somatosensory and motor regions. Data recorded from fNIRS suggest an increase in hemoglobin oxygenation in some participants in the right sensory region which was positively related to the degree of increase in swallowing rate. Thus subjects who experienced increased activation at the cortex with vibrotactile stimulation also increased their rate of swallowing with vibrotactile stimulation. As was mentioned earlier, it was likely that vibrotactile stimulation was not effective in penetrating deep into the larynx in at least some of the subjects because of variation in the amount of fat in the neck surface, possibly interfering with penetration of vibration to the mechanoreceptors in the laryngeal mucosa. This possibility is now being examined with a stronger motor and the maintenance of pressure on the vibrator along with caliper measures of the neck tissue.

Sidedness

A significant interaction was found between the effects of air puff and vibrotactile stimulation versus control with side and region of stimulation. In general stimulation effects were most notable in the left motor regions and the right sensory regions. Part of the differences in select regions showing a response had to do with the small number of participants we were able to obtain valid fNIRS responses in. This affected the right motor area, in particular, where only 5 subjects had valid fNIRS recordings in this region during vibrotactile stimulation significantly reducing statistical power. Only one subject had both valid vibrotactile and air puff fNIRS responses in this area, making statistical comparisons

impossible in this region. In the current study, the cortical areas measured were more likely to have suppression or activation on the right side. However, this may have been for technical reasons rather than demonstrating any laterality effect.

Differing responses of air puff and vibrotactile stimuli

Overall, the two types of stimulation had different effects on swallowing and blood oxygenation. Air puff stimulation enhanced swallowing and reduced blood oxygenation particularly in the right sensory region. No overall group effect occurred in the rate of swallowing with vibrotactile stimulation, and no significant change in oxygenation occurred with vibrotactile stimulation. As mentioned earlier some subjects showed an increase in oxygenation with vibrotactile stimulation in the right sensory region. The degree of increase in oxygenation in the right sensory area with vibration was significantly related to the degree of increase in swallowing rate overall for the group. This may have had to do with the limited effects of the vibrotactile motor used in this study.

The air puff stimulus seems to have greater effect on the swallowing center at the level of the brainstem compared to the vibrotactile device. The air puff stimulation seems to have an inhibitory effect on the cortical regions associated with swallowing while the vibrotactile stimulation has an excitatory effect, though not significant.

Clinical Implications

The results of this research support the idea that air puff stimulation induces swallowing in healthy adults. Air puff stimulation can be used in patients with feeding tubes who are not able to handle food and liquid boluses, giving additional sensory input. Air puff stimulation may hold significant potential as an intervention in swallowing therapy. However, the limitation of this approach is that it cannot be used with the application of a bolus to the oral cavity which would interfere with the application of air puff stimulation to

the faucial pillars. The findings of an inhibition at the cortex would further suggest that although air pressure stimulation of the faucial pillars is upregulating swallowing at the brainstem level, it might interfere with cortical activation for swallowing when applied concurrently.

The potential for cortical activation seen by vibrotactile device is important. If the vibrotactile device activates the cortex, the device could be used in targeted interventions aimed at enhancing voluntary swallowing control.

Study Limitations

A number of caveats need to be noted regarding the present study. The current investigation was limited by the sample size. More research needs to be undertaken before the association between the air puff and negative BOLD response is more clearly understood. The study consisted of 14 participants researchers were able to analyze the data of in the vibrotactile condition and only a small proportion (less than one-third) valid cortical recordings in all four regions. It is unknown if a significant increase in blood oxygenation with the vibrotactile stimulus would have been found with more subjects. As mentioned earlier it, is unknown whether the vibratory stimulus was of adequate intensity in all subjects to excite the mechanoreceptors in the laryngeal area.

The current study did not measure saliva. It is not known if the increase of swallowing seen by the air puff stimulus was due to increased salivation. Thirdly, the study did not control for food and liquid intake prior to participation in this study which could have influenced salivation rates and the level of hydration. Finally, the mouthpiece worn by the subjects was reported to be uncomfortable by some participants. The mouthpiece as worn during all conditions; the effects of the mouthpiece on the interaction of oral stimulation and salivation are unknown.

Future directions

This research has raised several questions in need of further investigation. A further study could assess the effectiveness of air puff stimulation in inducing swallowing in the dysphagic population secondary to stroke. Future studies could evaluate the relationship with air puff stimulation and the salivation rate.

The results of the fNIRS data suggest the vibrotactile device holds potential as a therapeutic device for voluntary swallowing and future studies are therefore recommended. Before a study done with vibrotactile stimulation on the dysphagic population is introduced, a study similar to this one should be carried out varying characteristics of the vibrotactile device. Further research should be done to investigate changes that could enable the vibrotactile device to elicit swallowing as seen by the air puff as the vibrotactile device can be used concurrently with ingestion of a bolus and might be application for swallowing retraining. Future studies should consider whether continuous stimulation would be more effective evoking swallowing than pulsed stimulation which was used here to assure comparable stimulation characteristics between the air puff and vibrotactile stimulation. Data are now being acquired on the ideal pressure at which the vibrotactile device can be applied to the outside of the larynx, and the effective strength of the vibrations. Research can also control for differing amounts of neck muscle and fat.

The issue of the negative BOLD response is an intriguing one which could be usefully explored in further research. It may be that the same stimulation, intraoral air pressure has opposing effects at the brainstem (excitatory) and cortex (inhibitory) as was suggested by the results here. It may be that one effect is reflexive at the brainstem in upregulating swallowing while the other is inhibitory for volitional responses at the cortex.

Further investigation is needed to address these issues on volitional swallowing control in both normal healthy adults and those with swallowing difficulties.

Appendix A

A Comparison of Vibrotactile and Air Puff Stimulation for Inducing Swallowing

Telephone Screening Questions

Name _____
Age _____
Phone Number _____
Person Who Contacted Subject _____

Qualifies for study
☐ Yes
☐ No
If yes, appointment is scheduled for:
_____

Parking pass mailed ☐ Yes
☐ NA

Hi, my name is _____ and I am calling from James Madison University's Neural Bases of Communication and Swallowing Laboratory about your interest in participating in our research study. How are you today? Is this a convenient time for us to be calling? Ok, great! Thank you so much for your interest. First, I need to ask you some questions to make sure you qualify for the study. You can answer with a yes or no. If I need more information I will ask you to elaborate. Are you ready?

Questions (Inclusion Answers in **BOLD**)		
• Have you ever had feeding or swallowing problems?	Yes	**NO**
• Have you ever been diagnosed or treated for reflux?	Yes	**NO**
(Inclusion = NO here or YES to follow-up question)		
▪ If yes, are you currently being treated for reflux?	Yes	No
▪ If yes, is your reflux controlled currently?	**YES**	No
• Are you right or left handed?	Right	Left
• Have you ever had complaints of globus? Globus is when you feel sensation of a lump or mass in the throat when no mass is present.	Yes	**NO**
• Have you been diagnosed with a neurological disorder, including but not limited to: stroke, dementia (such as Alzheimer's), Parkinson's disease, epilepsy, ALS, or multiple sclerosis?	Yes	**NO**
• Have you ever been hospitalized after a car accident or head injury?	Yes	**NO**
• Have you had or are you being treated for any psychiatric illnesses?	Yes	**NO**
• Have you ever had any speech problems?	Yes	**NO**
▪ If yes, could you explain your those problems		

- Do you have braces or a dental prosthesis? Yes **NO**
- Do you have any major health concerns? Yes **NO**
    - If yes, what are your health concerns?

In a minute I am going to ask if you would you be interested in participating in the near-infrared spectroscopy (NIRS) portion of the study as well. You have the option participating in the study with or without NIRS. All subjects in this study will receive air puff and vibrotactile stimuli during the experiment. Some participants will elect to also participate with the NIRS portion of the study. NIRS is a safe and non-invasive system used to measure your brain responses. Those participating in the NIRS portion of the study will receive a free anatomical MRI that will be read by a radiologist before the study to provide a brain map for identifying the target regions for NIRS recordings.

Participation in this study without fNIRS will require approximately 3 hours consenting to and participating in the experiment. The experiment will take one session and could be done after the consent process if time allows. Participation in this study with NIRS will require approximately 6 hours including the consent process, an MRI at RMH, and one experimental session lasting approximately 4 hours.
Are you interested in participating in the NIRS portion of our study? In order to do this you would receive an MRI at Rockingham Memorial Hospital and have your brain activity recorded via low-risk, non-invasive technology. (Inclusion = Yes or No)
If **NO** to NIRS and person qualifies for the study, proceed to schedule an appointment. The session should take approximately 3 hours.
If **YES** to NIRS and person qualifies according to first set of questions, ask the additional questions:

Now I am going to go over some exclusionary for participants undergoing MRI and fNIRS.
Please let me know with a yes or no if any of the following apply to you:

- Pregnancy Yes **NO**
- Cardiac problems
    - history of cardiac rhythm condition (including heart murmur or cardiac arrhythmia) Yes **NO**
    - cardiac pacemaker in place
- Highly-pigmented (dark) skin color. This is because dark skin interferes with light transmission for measuring the brain function using NIRS. Yes **NO**
- Presence of metal in the body that would prevent you from having an MRI (prostheses, electrodes, shrapnel, aneurism clips, other medical hardware) Yes **NO**
- Previous or current occupation as a metal workers (due to the possibility of unknown/undetected metal in their body) Yes **NO**
- Broken skin on the scalp Yes **NO**

• Claustrophobia	Yes	**NO**
• Previous surgery that used surgical staples	Yes	**NO**
• Artificial joints	Yes	**NO**
• Presence of certain tattoos with ferromagnetic metal or permanent makeup	Yes	**NO**

If all **NO,** schedule an appointment for the person to consent to the experiment with NIRS before scheduling an MRI at RMH.

Appendix B

Consent to Participate in Research

Identification of Investigators

You are being asked to participate in a research study conducted by Dr. Christy Ludlow (Primary Investigator) Sarah Heygi, Lara Karpinski, and Katie White (Co-Investigators), from James Madison University, Department of Communication Sciences and Disorders.

Purpose of the Study

The purpose of this study is to better understand the effects of two different stimuli on the frequency of swallowing and the response in the brain during stimulation. The findings of the study will contribute to our overall understanding of swallowing and could help people with swallowing disorders in the future.

Background

Safe swallowing requires the ability to control when you swallow and to protect your airway. A chronic swallowing disorder (dysphagia) can be life threatening, as it can place patients at risk for aspiration of liquids and/or solids into the trachea. Repeated aspiration of substances into the lungs can result in pneumonia.

Study Population

Up to 30 healthy volunteers will participate in this study.

Inclusion Criteria

You may be eligible for this research study if:

- You are between the ages of 18 and 60 years old
- You are in stable medical condition

Exclusion Criteria

Exclusionary criteria by participant report:

- History of swallowing complaints or problems
- History of diagnosis and/or treatment reflux
- Complaints of globus (sensation of a lump or mass in the throat when no mass is present)
- History of past brain injury, epilepsy, or neurological disorders (including stroke)
- Previous neck injury
- Psychiatric problems
- Speech problems
- Dementia, agitation, or a decreased level of alertness
- Diagnosis of progressive neurodegenerative disorders, such as dementia, Parkinson's Disease, multiple sclerosis, peripheral neuropathy, and amyotrophic lateral sclerosis

All subjects in this study will receive air puff and vibrotactile stimuli. Some participants will also receive an anatomical MRI before the study to provide a brain map to identify brain regions important for swallowing for functional near-infared spectroscopy (fNIRS) recordings.

Exclusionary criteria for participants undergoing MRI and fNIRS:

- Pregnancy
- Cardiac problems
    - history of cardiac rhythm condition (including heart murmur or cardiac arrhythmia)
    - cardiac pacemaker in place
- Highly-pigmented (dark) skin color, which interferes with the measurement of light transmission through the scalp
- Presence of metal in the body (prostheses, electrodes, shrapnel, aneurism clips, other medical hardware) that would prevent the participant from having an MRI
- Presence of certain tattoos with ferromagnetic metal or permanent makeup, due to the exposure to high magnetic force through MRI procedures
- Subjects who were metal workers as a previous occupation will also be excluded due to the possibility of unknown/undetected metal in their body
- Volunteers with the broken skin in the area that the fNIRS probes will be placed on the scalp
- Claustrophobia
- Previous surgery that used surgical staples
- Artificial joints

Research Procedures

Should you decide to participate in this research study, you will be asked to sign this consent form once all your questions have been answered to your satisfaction. If you decide to participate in this study, you may be assigned to either the pilot testing or the experimental study.

Pilot Test of the Effects of Air puff versus Vibrotactile Stimulation and fNIRS without MRI

Before the experiment starts, we will make a dental impression of your upper teeth to use later in the experiment.

We will attach a movement transducer device (about the size of a dime) to your neck with tape and will wrap bands around your rib cage and abdomen to measure your respiration.

To determine the effects of the air puff stimulation, we will place something similar to a mouth guard, made from the dental impression, in your mouth along your upper teeth with a small plastic tube. This tube will attach to a longer tube outside of the mouth,

which will attach to an air delivery device. You will have the tubing in their mouth for approximately 30 minutes before the experiment begins to allow for acclimation and during the two approximately 40 minute experimental periods. You will feel several series of air pulses from the tube onto the back of the mouth during the air puff stimulus condition of the experiment.

To determine the effects of a vibrator, the vibrotactile stimulation device (about the size of a dime) will be attached to the outside of your throat with tape and an elastic band. You will feel a series of vibrations to the throat when this is activated. There will be periods in which each of these devices is on, and periods when each device is off. Your oral secretions will be suctioned when necessary. The suctioning will be done by a licensed speech pathologist. We also may provide you with a very slow drip of artificial saliva to maintain your oral saliva at a controlled level throughout each 10 minute interval.

The participant will insert ear plugs to block out sound of vibrotactile and air puff stimuli during the experiment

Time Required

Participation in this study without fNIRS will require approximately 3 hours consenting to and participating in the experiment. The experiment could take one session and could be done after the consent process if time allows. Otherwise the participant will return for 1-2 sessions. Participation in this study with fNIRS will require approximately 6 hours including the consent process, an MRI at RMH, and 1-2 experimental sessions together lasting approximately 4 hours.

Experimental Study of the Effects of Air puff versus Vibrotactile Stimulation and fNIRS with MRI

After signing the informed consent, you will be asked to obtain a free MRI scan at Rockingham Memorial Hospital (RMH) which we will schedule for you.

If you are a female with child bearing potential we will need to be assured that you are not pregnant before undergoing a MRI scan. To determine if you have child bearing potential you will be asked the date of your last menses. To be considered post menopausal you will need to be over 1 year past your last menses. If you have child bearing potential, you will be provided with a pregnancy testing kit and required to take the test the morning of the scheduled MRI scan and to report the test result to the research staff at JMU by phone or in person before going to the RMH for scanning. If you have not reported a negative pregnancy test before a scan, the scan will be cancelled by the JMU staff by contacting the RMH prior to the scan.

The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will be on a table that can slide in and out of the cylinder. While in the scanner, you will hear loud knocking noises. You will be able to communicate with the MRI staff at all times during your scan. You may ask to be moved out of the machine at

anytime. The MRI does not involve radiation exposure because X-rays are not used.

After completing the MRI scanning you will return to James Madison University on another day to do the experimental study that will include the same procedures as the pilot testing procedures described above.

We will place the fNIRS probes on your scalp. Your hair will be parted and pinned back if needed with bobby pins or hair clips. The correct placement will be confirmed using Brainsight software which will allow us to identify the fNIRS targets using your MRI. A self-adherent elastic wrap will be wrapped around your head to hold the probes in place.

Risks, Inconveniences and Discomforts

Magnetic Resonance Imaging (MRI):
People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. You will be screened for these conditions prior to the study, and if you have any, you will not be able to participate in the study. If you have a question about any metal objects being present in your body, you should inform the physician. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

Women who are pregnant may not undergo a research MRI. Therefore, all women of childbearing potential will have a pregnancy test performed, which must be negative, before proceeding. Individuals with fear of confined spaces may become anxious during an MRI. The noise of the MRI machine may be too loud and affect your hearing. Therefore, trained professionals will place earplugs in your ears for this procedure. You will be asked to complete an MRI screening form, and to sign a separate MRI consent for each MRI. There are no known long-term risks associated with MRI scans. The main discomfort associated with the study is the need for the subject to remain quiet within the scanner for the duration of testing, about 20 minutes maximum.

When you register for the MRI at RMH they will ask you to sign a release for the radiologists to send the report to your primary care physician. If there are abnormal findings on the MRI you will be notified and the findings will be communicated with your primary care physician. Once you are notified that abnormal findings have been identified it will be your responsibility to follow-up with your primary care physician.

Air Puff Stimulus and Vibrotactile Stimulus
These are both non-invasive forms of stimulation which carry no known risks. You may feel a sensation similar to cool water on the back of your mouth from the air puffs. We will place something similar to a mouth guard, made from the dental impression, in your

mouth along your upper teeth with a small plastic tube. This may cause you to salivate more and for that reason we may suction at 10 minute intervals. You will feel a vibration on your throat with the throat stimulator.

Movement transducer device and Respitrace
These are both non-invasive and carry no known risks. The movement transducer device will be attached to the neck with tape which could cause brief skin irritation after removal. The Respitrace bands will be wrapped around your rib cage and abdomen during the experiment but should not cause any discomfort.

fNIRS
There is a risk of lasers being introduced to the eyes. However, these lasers are similar to a laser pointer and the risk is minimal. Also, crayon markers will be used on the scalp during probe during placement of the fNIRS sensors. These marks will wash away and no hair will be removed. Additionally, the sensors are slightly uncomfortable on the scalp as they are held in place with light pressure.

Benefits

There are no direct benefits to you from participating in this research. The results of this stimulation study will likely yield generalizable knowledge which might benefit others with dysphagia in the future. Some persons will also receive an MRI at RMH which will be read by a radiologist to identify any structural abnormalities which you will be informed about.

Confidentiality

Your participation in this study is entirely confidential. All data will be kept in a locked and secure location that can only be accessed by authorized investigators. The results of this project will be coded in such a way that your identity will not be attached to the final form of this study. Your identity will be disassociated from your data and you will be assigned a participant number. The researchers retain the right to use and publish non-identifiable data. The overall results of this research may be presented at professional conferences. You may sign a release form to obtain your results from this study and to allow use of your non-identifiable data for educational purposes here at JMU.

Compensation

You will be paid for your participation in this study. All participants will be paid $20 for the first hour of their time and $10 for every hour thereafter.

Participation & Withdrawal

Your participation is entirely voluntary. You are free to choose not to participate. Should you choose to participate, you can withdraw at any time without consequences of any kind. The investigator can remove you from the study at any time if continuation is not in your best medical interest or if you are unable to follow the study requirements..

Alternative Procedures

As you do not have a swallowing disorder, this is not a treatment study for you and no alternative procedures are available.

Questions about the Study

If you have questions or concerns during the time of your participation in this study, or after its completion or you would like to receive a copy of the final aggregate results of this study, please contact:

Sarah Heygi, Lara Karpinski,
and Katie White
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Questions about Your Rights as a Research Subject

Dr. David Cockley
Chair, Institutional Review Board
James Madison University
(540) 568-2834
cocklede@jmu.edu

Giving of Consent

I have read this consent form and I understand what is being requested of me as a participant in this study. I freely consent to participate. I have been given satisfactory answers to my questions. The investigator provided me with a copy of this form. I certify that I am between 18– 60 years old.

☐ I give consent to participate in Pilot Testing (Behavioral training only) _____ (initials)

☐ I give consent to participate in Experimental Study (Behavioral training + fNIRS)
_____ (initials)

_____
Name of Participant (Printed)

_____ _____
Name of Participant (Signed) Date

_____ _____
Name of Researcher (Signed) Date

_____ _____
Name of Witness (Signed) Date

Appendix C

Edinburgh Handedness Inventory

Your Initials:_____

Please indicate with a check (✓) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put two checks (✓✓).

If you are indifferent, put one check in each column (✓ | ✓).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

Task / Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking a Match (match)		
10. Opening a Box (lid)		
Total checks:	LH =	RH =
Cumulative Total	CT = LH + RH =	
Difference	D = RH – LH =	
Result	R = (D / CT) × 100 =	
Interpretation: (Left Handed: R < -40) (Ambidextrous: -40 ≤ R ≤ +40) (Right Handed: R > +40)		

Appendix D

Release to Obtain Information

I wish to receive my personal results from this study. I give permission for the investigators of the Neural Bases of Communication and Swallowing Laboratory to release my personal data for my personal records.

☐ I wish to obtain my data electronically via email.
My email address is _____

☐ I wish to obtain my data via US mail.

My permanent address is _____

_____

_____
Name (Printed) Date

_____
Name (Signed) Date

I **do not** wish to receive my personal results from this study. I **do not** give permission for the investigators of the Neural Bases of Communication and Swallowing Laboratory to release my personal data for my personal records.

_____
Name (Printed) Date

_____
Name (Signed) Date

Appendix E

Release of Data for Educational Use

I give permission for the investigators of the Neural Bases of Communication and Swallowing Laboratory to use my individual data for educational purposes at James Madison University and professional conferences (Your data will NOT reveal any personally identifying information).

_____

Name (Printed) Date

_____

Name (Signed) Date

I **do not** give permission for the investigators of the Neural Bases of Communication and Swallowing Laboratory to use my individual data for educational purposes at James Madison University and professional conferences

_____

Name (Printed) Date

_____

Name (Signed) Date

Appendix F

Permission for Future Contact Release Form
Laboratory of Neural Bases of Communication and Swallowing

I, _____, have been informed and understand that _____ in the Laboratory of Neural Bases of Communication and Swallowing at James Madison University is conducting a research study for the advancement of the field of speech-language pathology.

Please choose from the following:

☐ I give _____ (investigators) in the Laboratory of Neural Bases of Communication and Swallowing at James Madison University permission for future contact. I am aware that this future contact may include thank you letters, advertisements for future studies in this lab, and the research manuscript that will be submitted for publication.
You may contact me via (Check any that apply):

☐ Email address: _____

☐ Mail to home address: _____

_____

☐ Telephone number: _____

_____
Name (Printed) Date

_____
Name (Signed) Date

☐ I **do not** give _____ (investigators) in the Laboratory of Neural Bases of Communication and Swallowing at James Madison University permission for future contact. I **do not** wish to receive thank you letters, advertisements for future studies, or a copy of the research manuscript that will be submitted for publication.

_____
Name (Printed) Date

_____
Name (Signed) Date

Appendix G

Permission for Future Contact Release Form
Communication Sciences and Disorders Department

I, _____, have been informed and understand that there are other research laboratories in the Communication Sciences and Disorders Department at James Madison University conducting research studies for the advancement of the fields of speech-language pathology and audiology.

Please choose from the following:

☐ I give investigators in other research laboratories in the Communication Sciences and Disorders Department at James Madison University permission for future contact about future research studies. I am listing family members that may be interested in learning about participating in future studies.

You may contact me via (Check any that apply):

☐ Email address: _____

☐ Mail to home address: _____

_____

☐ Telephone number: _____

_____
Name (Printed) Date

_____
Name (Signed) Date

☐ I **do not** give investigators in other research laboratories in the Communication Sciences and Disorders Department at James Madison University permission for future contact about future research studies.

_____
Name (Printed) Date

_____

Name (Signed) Date

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